Vaccines and Related Biological Products Advisory Committee

Meeting Date: December 17, 2002

FDA Clinical Briefing Document for

MedImmune Vaccines Inc.
Cold Adapted Influenza Vaccine, Trivalent - FluMist?

ChrisAnna Marie Mink, M.D.
Antonia Geber, M.D.
Douglas Pratt, M.D.

Table of Contents

1.0 INTRODUCTION

1.1 Description of Product

FluMist? Influenza Virus Vaccine, Trivalent A & B Live, Cold Adapted (FluMist) is an intranasal vaccine for active immunization for the prevention of influenza. FluMist contains three strains of live, attenuated, cold-adapted, temperature-sensitive influenza virus: two Type A (H1N1 and H3N2) and one Type B. Each 0.5 ml dose contains approximately 10^7 $TCID_{50}$ of each of the three strains of influenza in normal allantoic fluid (NAF) containing sucrose-phosphate-glutamate (SPG).

1.2 Indication Sought

The sponsor has proposed the following label indication, "FluMist? is indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children, adolescents and adults, 5 years through 64 years of age." The requested dosing regimens: for the first use in children 60 months through 8 years, two 0.5 ml doses given at least one month apart should be administered. For those previously immunized against influenza and for individuals 9 years through 64 years of age, one 0.5ml dose should be given.

In the original Biological License Application (BLA), the requested age range was from 12 months to 64 years of age. The sponsor revised the proposed age range to 19 months to 64 years of age on March 15, 2002, and then to 5 years through 64 years of age on November 1, 2002. Also in the original BLA, an indication was sought for travelers to areas with circulating influenza viruses, but this request has been removed.

1.3 Regulatory History

The chronology of regulatory review is presented in Table 1.3a.

Table 1.3a Chronology of Regulatory Review

Biological License Application submitted by the sponsor[1]	October 30, 2000
VRBPAC[2] Meeting	July 26 - 27, 2001
CBER issued complete review letter #1	August 31, 2001
Sponsor submitted complete response to CBER's CR letter #1	January 7, 2002
CBER issued complete review letter #2	July 10, 2002
Sponsor submitted complete response to CBER's CR letter #2	August 26, 2002
Sponsor revised indication for age range	November 1, 2002
VRBPAC Meeting	December 17, 2002

[1]Aviron was purchased by MedImmune Inc. in January 2002, and became MedImmune Vaccines, Inc., a wholly owned subsidiary of MedImmune, Inc. Throughout this document, the sponsor will be referred to as MedImmune, including the laboratory location in Mountain View, California.
[2]Vaccines and Related Biological Products Advisory Committee

The original BLA was submitted to FDA/CBER on October 30, 2000. The available safety and efficacy data submitted in support of the BLA were presented to VRBPAC in July 2001. At that time, the committee voted (8 yes and 7 no) that the efficacy data were adequate to support licensure in children, age one through 17 years. Five of the seven committee members who voted "no" qualified that they would have likely voted "yes" if the sponsor was seeking an indication starting in older children at 15 months or 24 months of age. The committee voted (13 yes and 2 no) that the efficacy data were adequate to support licensure in adults, age18 years through 64 years. Although the vote for efficacy was favorable, the committee expressed several concerns about the efficacy data, including 1) availability of data from few subjects younger than 2 years or over 50 years of age, 2) the use of effectiveness data (in contrast to an assessment of efficacy with culture-proven influenza) to support use in the adult population, 3)

uncertainty about the necessary number of doses and the optimal interval for the two-dose regimen for children younger than 9 years of age, and 4) no data for concomitant immunization with FluMist and any other vaccines.

The committee voted that the safety data were not adequate (5 yes and 9 no votes) to support licensure in individuals, 12 months through 64 years of age. The primary concerns cited were that the database was incomplete and CBER's review was on-going. Thus, the committee expressed concerns that they did not have a full understanding of the safety profile following receipt of FluMist. Other concerns included: 1) the lack of safety data for concomitant use of FluMist with other vaccines, especially for routinely recommended pediatric vaccines in children younger than 2 years of age, 2) possible association of FluMist with adverse respiratory events including pneumonia and asthma/wheezing, 3) insufficient data assessing shedding and transmissibility of vaccine viruses, 4) few subjects in the extreme age groups (younger that 2 years and older than 50 years of age), and 5) the possibility of reassortment, including with wild type strains, and the risk of reversion to virulence of the attenuated vaccine strains.

Since July 2001, CBER has issued two complete response letters (CRLs) requesting additional information and clarifications, including a finalized database with Complete Study Reports as supportive for the BLA. The sponsor has provided responses to the CRLs from CBER. At the December 2002 VRBPAC meeting, additional safety analyses will be presented, and available efficacy and effectiveness data will be reviewed for the committee to consider in its deliberations.

2.0 UNRESOLVED SAFETY CONCERNS

2.1 Number of Subjects Exposed to the Product in the Final Database

The total number of subjects, in all age groups, who had received one or more doses of FluMist in clinical trials was not clear at the time of the July 2001 VRBPAC meeting. Subsequently, a finalized list of the clinical trials considered by the sponsor to be supportive for licensure (Table 2.1a) and a table showing the number of subjects who participated in these trials (Table 2.1b) have been provided. A total of 20 trials, 14 randomized, double-blind, placebo-controlled [including three trials considered as pivotal (AV006, AV009 and AV019) by the sponsor], and six open-label trials have been submitted. Of note, three studies (**AV017**, the fourth year dosing of FluMist for subjects in the Pediatric Efficacy trial (AV006); **AV018,** the concomitant administration of FluMist with MMR? and VARIVAX? ; and **VA448**, the Veterans' Administration-sponsored trial of FluMist when given with inactivated influenza vaccine to adults with chronic obstructive pulmonary disease) included in the original BLA have been removed from the database because the studies are not yet completed and/or the finalized study reports are not available. Also, **D145-P500**, a study of transmissibility of FluMist in a daycare setting, sponsored by Wyeth–Lederle Vaccines, has been added to the database.

Table 2.1a Final Summary of Clinical Trials with FluMist Submitted in the BLA.

PEDIATRIC TRIALS						
Protocol Number	**Phase**	**Study Goal**	**Age Range**	**Total**	**FluMist**	**Placebo**
AV002	I/II	Dose Escalation	18-71 months	238	155	83
AV002-2	II	Dose Escalation	18-71 months	118	79	39
AV006	III Pivotal	Efficacy against Culture Confirmed Influenza	15-71 months	Yr 1, 1602 Yr 2, 1358	1070 917	532 441
AV007	III Pivotal	Lot Consistency Study	12-36 months	500	Consistency lots, n=300; efficacy lot, n=100	100
AV010	II/III	Safety in Asthmatics	9-17 yrs	48	24	24
AV011	III Pivotal	Challenge of Subset of AV006 subjects with Vaccine Strain H1N1	34-91 months	222	CAIV-M	-
AV012	III Non-pivotal	Herd Immunity Trial	18 mo – 18 years	Yr 1, 4298 Yr 2, 5251[a]	4298 5251	- -
AV014	III Pivotal	Consistency from Two Manufacturing Facilities	12-42 months	225	225	-
AV015	III Non-pivotal	Safety of Re-vaccination in Yr 3 of Subset of AV006	3-8 years	949	949	-
AV019	III Pivotal	Safety Assessment in Northern California Kaiser Permanente	1-17 years	9689	6473	3216
AR001[a.]	II	Safety of Classical vs. Recombinant Processes for Preparation of FluMist	6 months and over	65 – children 449 - total	65	-
Wyeth D145-P500	II/III	Transmissibility of FluMist in Daycare Setting	≥ 8 mo < 36 mo	197	98	99
ADULT TRIALS						
AV001	I	Phase I/II spray *vs*. drops	18-65 years	239	181	58
AV003	III	Efficacy Against Investigational Challenge with Wild Type Influenza	18-40 years	103, 92 challenged	36 (TIV=33)	34
AV004	II	Safety	18-65 years	20	15	5
AV005	II	Safety of 2 doses	18-45 years	32	16	16
AV008	II/III	Safety in elderly, high risk	≥ 65 years	200	100	100
AV009	III Pivotal	Safety and Effectiveness in Healthy Adults	18-64 years	4561	3041	1520
AR001[a]		As above				
DMID #98-005	II	Safety in HIV-infected compared to HIV-negative Adults	18-40 years	111, Infected, n=57 Negative, n=54	55	56

a – Children and adults participated in this protocol. Table generated by CBER.

Table 2.1b Total Number of Doses of FluMist and Placebo Administered (by Age Group) in Trials with Completed Clinical Study Reports Submitted in the BLA.

	Doses of FluMist[a]						Doses of Placebo Total
Age Category	**First**	**Second**	**Third**	**Fourth**	**Fifth**	**Total**	
1-2 years	1285	256				1541	730
2–4 years	4678	2889	475	188	1	8231	2593
5–8 years	4418	2643	365	367	1	7794	1970
9–17 years	5903	1028				6931	1371
18–29 years	1081	29				1110	458
30–49 years	2241	9				2250	1037
50–64 years	511					511	209
65 years and up	111					111	101
Total All Studies[b]	**20228**	**7354**	**840**	**555**	**2**	**28979**	**8469**

[a]The fourth and fifth doses represent vaccination for a third annual season.
[b]Includes 171 children in Studies AV002 and AV002-2 who received 10^4, 10^5, and 10^6 $TCID_{50}$ dosages rather than 10^7 $TCID_{50}$, 28 HIV-infected adults in Study DMID #98-005, and 24 children 9-17 years with moderate to severe asthma in AV012.
Table adapted from MedImmune, November 2002.

2.2 Summary of Newly Submitted, Finalized Trials

At the time of the July 2001 meeting, studies with incomplete study reports included AV019, the large safety trial in Northern California Kaiser Permanente (NCKP), and AV012, a Herd Immunity Trial in Texas. Final study reports for these two trials have been submitted. Also, no studies to assess the transmissibility of FluMist viral strains were included in original BLA. In January 2002, a clinical study report (CSR) for the Wyeth-Lederle sponsored trial D145-P500 to assess shedding and transmission was submitted. These trials are summarized below.

2.2.1 Study AV019: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Safety of Frozen FluMist in Healthy Children and Adolescents.

AV019 – Study Design

Study AV019 was conducted to provide safety data with FluMist in children and adolescents. In a double-blind fashion, healthy children ages 12 months through 17 years were randomized in a 2:1 ratio to receive FluMist or placebo in 32 outpatient clinics in the NCKP system, a health maintenance organization (HMO). Children less than 9 years of age received 2 doses of study vaccine (28-42 days apart) and individuals 9 -17 years of age received one dose of study vaccine. The original protocol planned for enrollment of 15,000 subjects, though the final enrollment was approximately 9700 subjects.

Vaccines

The study was initiated in October 2000, but the influenza strains contained in FluMist were the 1999-2000 strains, including A/Beijing/262/95 (H1N1), A/Sydney/05/95 (H3N2) and B/Yamanashi/166/98. The influenza strains recommended for 2000-2001, included the same B strain; however, both of the A strains were different. The placebo was normal allantoic fluid (NAF).

Inclusion/Exclusion Criteria Related to Asthma
Subjects with a history of asthma or possible asthma as reported by the parent/guardian were to be excluded from study participation.

Safety Monitoring
Medically attended events (MAEs) and serious adverse events (SAEs) were the primary safety outcomes. The primary method of ascertainment of the safety outcomes (MAEs and SAEs) was extraction of records from the NCKP computerized health care utilization databases. Outcomes were also collected via spontaneous reporting of parents/guardians, though these reports were not systematically evaluated. Active monitoring for solicited reactogenicity events post-vaccination was not performed.

The occurrence of SAEs and MAEs were monitored during the safety assessment period. For each participant, the safety monitoring period was defined as follows: for Dose 1, the observation began on the day of vaccination (Day 0) and ended at the earliest of:

a) Dose 2 (generally 28 days later, for subjects 1-8 years of age) or
b) Day 42 post-vaccination.

For subjects in the two-dose regimen, the safety monitoring period after Dose 2 began on the day of vaccination with Dose 2 and ended on Day 42 post-vaccination.

SAEs were defined consistently with 21 CFR 312 including 1) death, 2) immediately life-threatening, 3) results in persistent or significant disability, 4) results in or prolongs an existing hospitalization, and 5) is a congenital anomaly or birth defect. Additionally, an important medical event that may not have resulted in death or been life-threatening or required hospitalization, may have been considered an SAE based upon appropriate medical judgment if it jeopardized the participant and may have required medical intervention to prevent one the listed outcomes.

MAEs were defined as an encounter with a health care provider, such as a visit to a medical clinic, emergency department (ED), or a hospital admission. The MAEs reflect the coded diagnoses assigned by the health care provider who saw the child at presentation, as recorded on the standardized NCKP encounter forms. One or more MAEs may have been assigned for a single encounter.

AV019 - Statistical Methods
The primary objective of the study was to provide incidence estimates for a variety of MAEs, including SAEs, in FluMist recipients relative to placebo recipients. Safety outcomes were expressed as relative risk estimates with 90% confidence intervals (CI). The sponsor notes that due to the exploratory nature of the study, large numbers of CIs were constructed without multiplicity adjustments. Pre-specified analyses were performed by age group (all participants, 1-8 years, 9-17 years, 12-17 months and 18-35 months) and by dose (after Dose 1, after Dose 2, and after all doses combined).

MAEs were analyzed by individual coded diagnosis within the following pre-specified classes of events: acute respiratory events, systemic bacterial infections, acute gastrointestinal events and rare, potentially wild type influenza-related events.

A two-stage approach was used for the analysis of MAEs:

a) Binomial screening – in this analysis, participants experiencing multiple encounters for the same MAE were counted once. The relative risks (RR) with 2-sided 90% CI was presented. RR= rate in FluMist / rate in placebo, and the CI was constructed using mid-probability binomial method, adjusted for follow-up time.
b) Poisson regression - for all MAEs with lower bound of the 90% CI exceeding 1, Poisson regression was performed. The number of encounters per participant for each MAE was modeled as a Poisson random variable with treatment group, age category (1-17 years, 3-8 years, 18 to < 36 months and 12 to < 18 months), gender and race included as classification variables. The RRs for treatment group with 90% CI were calculated.

Results were presented separately for clinic visits, ED visits, and hospitalizations.

The sample size of 9700 subjects provided ~85% power to rule out a four-fold increase in events that occurred at 1 per 1000 in the placebo subjects. The power calculations were computed by simulation using a normal approximation with continuity correction, evaluating the lower bound of a 2-sided 90% CI on the proportion of rates, FluMist/placebo. Although the age group analyses were defined prospectively, the sample size was not adequate to permit ruling out significant differences between the treatment groups for most of the planned comparisons.

Interim Analysis

An interim analysis of safety was completed in April 2001, in order to provide an interim safety summary to CBER. No changes in the conduct of the study were planned or reported as a result of this analysis. The interim analysis required unblinding of the study and was performed according to the Data Analysis Plan (DAP).

AV019 - Results

A. Enrollment and Demographics

Between October 2, 2000 and December 22, 2000, 9734 participants were enrolled and 9689 (FluMist n=6473 and placebo n=3216) were evaluable for safety. Of the enrollees, 5637 (58%) were from 1-8 years and 4052 (42%) were from 9-17 years old. The demographics for the FluMist and placebo groups were similar with respect to age (mean age = 8.1 years), gender (51% female) and race/ethnicity (55% white, 50% Hispanic, 10% Asian/Pacific Islander and 5% each African American, multiracial or other).

Approximately 87% of 5637 subjects 1-8 years of age (FluMist n=3781 and placebo n=1889) in the 2-dose regimen received the 2nd scheduled dose of vaccine. The most common reasons reported for not receiving the 2nd vaccination were:

- Unable to contact (FluMist – 55.6%, placebo – 47.6%) and
- Non-compliance (FluMist – 35.1%, placebo – 37.4%).

Thirty-nine FluMist recipients (7.7%) and 27 placebo recipients (10.6%) did not receive Dose 2 due to an AE observed after Dose 1. The most common reason for refusing the second dose cited by parents was “child became ill” after the first dose. Thirty eight (FluMist, n=20 and placebo, n=18) Dose 2 refusals were reported, and the majority of symptoms described by both treatment groups were related to the respiratory tract, e.g. asthma, otitis media, croup, pneumonia and URI. Not all of the illnesses leading to refusal of Dose 2 resulted in an MAE captured in the database searches.

B. SAEs

No deaths among the study participants were reported. In the 42-day post-vaccination period, 20 SAEs occurred, at a rate of 0.2% in both the FluMist and placebo recipients (FluMist, n=13

and placebo, n=7), as shown on Table 2.2.1a. Eleven SAEs were hospitalizations and six additional SAEs were psychiatric hospitalizations. The remaining three included an ED visit for trauma in a placebo recipient, an outpatient diagnosis of synovial carcinoma and surgery for a benign foot lesion (both in FluMist recipients). In the FluMist group, four of the 13 SAEs occurred within 14 days of vaccination, and all but one (hospitalization for hemolytic-uremic syndrome) of the events occurred after Dose 1.

Table 2.2.1a Serious Adverse Events Reported from Day 0-42 Post-vaccination in Participants in Study AV019

Age/Gender	Treatment Group	Vaccination Date	Days Since Vaccination	Diagnosis
5y Female	Placebo	01-03-01	25	Diabetes[1]
6y Female	Placebo	10-23-00	29	Suicide Ideation[2]
1y Female	Placebo	10-04-04	4	Trauma/pre-existing Hemophilia[3]
1y Female	FluMist	11-17-00 (Dose 2)	11	Hemolytic-uremic syndrome[1]
5y Male	FluMist	10-23-00	22	Upper airway obstruction[1] Post-extubation
1y Female	FluMist	01-05-01 (Dose 2)	11	Acute gastroenteritis[1]
6y Male	Placebo	12-22-02	39	Dehydration[1]
5y Female	Placebo	11-17-00 (Dose 2)	9	Cellulitis/Fractured clavicle[1]
1y Female	Placebo	11-15-00	4	Croup[1]
12y Female	FluMist	11-30-00	15	Benign foot lesion[4]
16y Male	FluMist	11-16-00	20	Suicide attempt[2]
12y Female	Placebo	12-01-00	4	Psychiatric disorder[2]
16y Female	FluMist	10-06-00	32	Danger to self and others[2]
14y Female	FluMist	10-03-00	30	Depressive disorder with Psychotic features[2]
10y Male	FluMist	10-12-00	36	Bipolar Disorder/ Post-traumatic Stress disorder[2]
12y Female	FluMist	12-4-00	42	Appendectomy for rule-out Appendicitis*[1]
16y Female	FluMist	11-14-00	10	Abdominal pain /gynecologic disorder[1]
15y Male	FluMist	10-18-00	11	Appendicitis/ appendiceal abscess[1]
9y Male	FluMist	12-08-00	36	Testicular torsion[1]
16 y Male	FluMist	10-30-00	21	Synovial sarcoma[4]

[1]Hospitalization
[2]Psychiatric hospitalization
[3]Emergency Department (ED) visit
[4]Outpatient clinic visit
* Appendix without significant inflammation on histopathologic examination
Table adapted from MedImmune January CR responses, Volume 14.

C. MAEs

In the interim analysis presented by Dr. Steve Black at the July 2001 VRBPAC meeting, an increase in asthma events was noted for children 18-35 months of age; this finding is discussed in more detail below. Of note, no increase in pneumonia or bronchitis was identified.

The number of subjects who experienced at least one MAE is shown in Table 2.2.1b.

Table 2.2.1b AV019 - Subjects who experienced an MAE by utilization setting.

Utilization Setting	FluMist, N=6473 n (%)	Placebo, N=3216 n (%)
Hospital[a]	31 (0.5)	19 (0.6)
ED	186 (2.9)	104 (3.2)
Clinic	2305 (35.6)	1191 (37.0)

[a]Hospitalizations less than 24 hours were not necessarily reported as SAEs.
Table from MedImmune, January 2002 CR responses, Volume 14, page 48.

D. Pre-Specified Group Diagnoses

For the analysis of all utilization settings, doses and ages combined, none of the four pre-defined grouped diagnoses (acute respiratory tract events, systemic bacterial infections, acute gastrointestinal events, and rare events potentially related to influenza) occurred at significantly increased rates in the FluMist recipients compared to the placebo recipients. In this combined analysis, acute respiratory tract events were decreased among FluMist recipients [RR = 0.9 (0.82, 0.98)]. Because no systemic bacterial infections were reported, RR and CIs could not be calculated.

When the four pre-specified grouped diagnoses were analyzed by separate utilization settings, age groups and doses (n=113 analyses), 16 analyses identified events that were significantly decreased and two analyses identified event rates that were significantly increased in FluMist recipients compared to placebo recipients. The two events rates that were increased were 1) acute respiratory tract events in 9-17 year olds in the ED and 2) acute GI tract events in 9-17 years olds in the ED. For each of these two grouped diagnoses categories, 10 events occurred in FluMist recipients compared to 0 in the placebo recipients, and the lower bound of the 90% CI = 1.92. The event rates in the remaining analyses were neither significantly increased nor decreased.

E. Individual MAEs Associated with Increased Risk

The sponsor performed analyses of individual MAEs in a systematic way based upon: biological plausibility, the number and types of analyses associated with significantly increased or decreased risk, and in some cases, an analysis of temporal clustering within the 42 days post-vaccination.

Fourteen individual MAEs were associated with an increased risk in FluMist recipients. The sponsor considered a biological association to be implausible for eight of the 14, including benign lesions, elective procedure, enuresis, speech delay, UTI, seborrhea, otitis externa and warts. The remaining six were considered biologically plausible and included upper respiratory tract infection (URI), musculoskeletal pain, asthma, abdominal pain, otitis media with effusion (OME) and adenitis/adenopathy.

Asthma

The interim analysis of AV019 identified an increased risk of asthma in children 18-35 months of age. In analyses of the complete database, significantly increased risk of asthma was associated with receipt of FluMist in subjects18-35 months of age in four analyses, as shown in Table 2.2.1c.

Table 2.2.1c Increased Relative Risk for Asthma Events by Age Group and Setting

			Number Events*/ Number of Participants		
Age	**Setting**	**Dose**	**FluMist N=728**	**Placebo N=369**	**Binomial Risk (90% CI)**
18-35 mo	Clinic	1	10/9	0/0	--- (1.74, NA)
18-35 mo	Clinic	Both	17/15	2/2	3.81 (1.2, 16.82)
18-35 mo	All	1	11/10	0/0	--- (1.95, NA)
18-35 mo	All	Both	18/16	2/2	4.06 (1.29, 17.86)

*Two FluMist subjects had more than one asthma event.
NA = not available due to 0 events in placebo subjects.
Table generated by CBER.

Eighteen subjects (16 FluMist and 2 placebo) ages 18-35 months had 20 asthma events post-vaccination. Two FluMist subjects reported two asthma events. No hospitalizations were reported due to asthma events. Eleven asthma events (10 in the clinic and 1 in the ED) occurred in 10 FluMist recipients occurred following Dose 1. All subjects with an asthma event had a concurrent respiratory tract diagnosis (e.g. URI, bronchitis, acute otitis media, croup) and all subjects were given treatment. The therapies included beta-agonists for 94% (17/18) of subjects [FluMist 16/16 (100%) and placebo ½ (50%)], antibiotics for 56% (10/18) of subjects [FluMist 10/16 (63%) and placebo 0%], systemic corticosteroids for 33% (6/18) subjects [FluMist 5/16 (31%) and placebo 50%] and inhaled steroids for 17% (3/18) subjects [FluMist 3/16 (19%) and placebo 0%]. No apparent temporal clustering of events in the 42 days post-vaccination was observed.

Although a parental history of asthma was an exclusion criterion, review of databases identified that seven of the 16 (44%) FluMist subjects and none of the two placebo recipients with asthma events had a prior history of asthma, wheezing or reactive airway disease (RAD).

In the youngest age group, 12-17 months, no statistically significant increased risk of asthma events was identified in FluMist recipients (n=169). To assess for any association of age with risk for asthma following receipt of FluMist, asthma event rates following Dose 1 were examined by age in increasing increments of 6 months in a post-hoc analysis (Table 2.2.1d). Using this approach, the RR point estimates increased, as older children were included in the analysis, peaked in the12 to 59 month age group [RR = 3.53 (1.1, 15.66)] and declined thereafter.

No statistically significant increase for RR following Dose 2 was observed. Following both doses combined, the RR was significantly increased for the 12 – 53 month age group [RR=2.15 (1.10, 4.49)], which primarily reflects the event rates following Dose 1.

Table 2.2.1d Number of Asthma Events, Incidence Rates, and Relative Risks By Dose for All Participants by Cumulative Age Group (< 9 years).

Study	Age (months)	42 Day Summary Period		
		FluMist n/N (Rate)	Placebo n/N (Rate)	Relative Risk (90% CI)
AV019 Dose One	12–17	1/172 (4.98)	2/92 (18.57)	0.27 (0.02, 2.31)
	12–23	5/383 (11.11)	2/213 (8.08)	1.37 (0.35, 6.92)
	12–29	10/637 (13.37)	2/329 (5.22)	2.56 (0.76,11.70)
	12–35	11/904 (10.41)	2/465 (3.68)	2.83 (0.85,12.80)
	12–41	11/1196 (7.88)	2/630 (2.73)	2.89 (0.87,13.09)
	12–47	11/1465 (6.45)	2/771 (2.23)	2.90 (0.87,13.12)
	12–53	12/1750 (5.89)	2/893 (1.92)	3.06 (0.94,13.77)
	12–59	**14/2032 (5.92)**	**2/1025 (1.68)**	**3.53 (1.10,15.66)**
	12–65	14/2278 (5.30)	4/1144 (3.01)	1.76 (0.71, 4.92)
	12–71	16/2470 (5.58)	4/1251 (2.75)	2.03 (0.83, 5.60)
	12–77	20/2715 (6.34)	5/1377 (3.12)	2.03 (0.92, 4.97)
	12–83	21/2931 (6.16)	5/1489 (2.88)	2.13 (0.97, 5.20)
	12–89	21/3137 (5.76)	6/1597 (3.23)	1.78 (0.85, 4.04)
	12–95	21/3355 (5.38)	7/1705 (3.53)	1.53 (0.76, 3.28)
	12–101	22/3578 (5.29)	8/1798 (3.82)	1.38 (0.71, 2.84)
	12–107	23/3791 (5.22)	8/1894 (3.63)	1.44 (0.74, 2.94)
AV019 Dose Two	12–17	0/142 (0.00)	1/73 (9.70)	0 (0.00, 4.63)
	12–23	1/325 (2.18)	2/178 (7.95)	0.27 (0.02, 2.36)
	12–29	2/533 (2.66)	3/269 (7.89)	0.34 (0.06, 1.65)
	12–35	7/764 (6.49)	3/390 (5.44)	1.19 (0.38, 4.24)
	12–41	14/1019 (9.73)	4/525 (5.39)	1.80 (0.73, 5.04)
	12–47	17/1244 (9.67)	5/637 (5.56)	1.74 (0.77, 4.32)
	12–53	20/1488 (9.51)	5/744 (4.76)	2.00 (0.90, 4.89)
	12–59	23/1729 (9.42)	8/861 (6.58)	1.43 (0.74, 2.92)
	12–65	23/1948 (8.36)	9/957 (6.66)	1.26 (0.66, 2.48)
	12–71	25/2113 (8.37)	11/1051 (7.41)	1.13 (0.63, 2.10)
	12–77	25/2320 (7.63)	12/1157 (7.34)	1.04 (0.59, 1.89)
	12–83	26/2496 (7.37)	13/1254 (7.34)	1.00 (0.58, 1.79)
	12–89	27/2674 (7.15)	13/1347 (6.83)	1.05 (0.60, 1.86)
	12–95	27/2862 (6.68)	13/1437 (6.40)	1.04 (0.60, 1.85)
	12–101	27/3061 (6.24)	13/1517 (6.07)	1.03 (0.59, 1.83)
	12–107	27/3242 (5.90)	14/1600 (6.19)	0.95 (0.56, 1.66)

Note: Confidence intervals (CI) computed using Mid-p exact binomial method. A significantly increased risk is defined by the lower bound of the CI >1.0.
NA = not available due to 0 events occurring in placebo recipients.
Table from MedImmune, August 2002 CR response #43, Volume 3, page 132.

No increased risk of asthma in children between 60 and 107 months of age after a first or second dose as well as between 9 and 17 years of age after a single dose was observed.

Because the coded diagnosis of asthma may not detect some wheezing events, especially in young children, rates of events coded as wheezing and shortness of breath (SOB) were also evaluated. The event rates for wheezing/SOB were not significantly increased in any of the comparisons, including in the 18-35 month age group (Table 2.2.1e). In the youngest age group (12-17 month old), the RR for wheezing/SOB was 2.09 (0.35, 25.55), though few subjects in this age group were available for analysis.

Table 2.2.1e Study AV019 - Rates and Risks for Wheezing/Shortness of Breath by Age Group, All Doses and All Settings Combined.

Age	Number of Participants with Event/Number in Age Group		Rate per 1000-person months[a] FluMist/Placebo	Binomial RR[a] (90% CI)
	FluMist n/N	Placebo n/N		
12-17 months	4/171	1/90	10.04/4.481	2.09 (0.35, 25.55)
18-35 months	7/728	5/369	4.07/5.72	0.71 (0.27, 1.98)
1-8 years	30/3769	20/1868	3.37/4.54	0.74 (0.46, 1.21)
9-17 years	3/2704	3/1347	0.8/1.6	0.50 (0.12, 2.13)
1-17 years	33/6473	23/3216	2.6/3.66	0.71 (0.46, 1.12)

[a]Based upon participant-incidence
Table adapted from MedImmune, January 2002 CR responses, Volume 14, page 69.

Subjects with History of Asthma

A post-hoc analysis of subjects with a history of asthma (as identified by a database search for "asthma") was performed to determine event rates and RRs for selected respiratory events, including asthma, wheezing/SOB, pneumonia, bronchitis and croup. A total of 8.8% (852/9689) of participants had a prior diagnosis of asthma: 8.5% (552/6473) of FluMist subjects and 9.3% (300/3216) placebo subjects. Of the subjects with a history of asthma, 75% of the subjects were 1 through 8 years of age, in contrast to ~58% of total enrollees being in this age group.

For participants with a previous coded diagnosis of asthma, events with a statistically significant increased risk following FluMist are shown in Table 2.2.1f. Although an increased risk for croups was noted for subjects 1-17 years of age, all of these events occurred in subjects 1-8 years of age.

Table 2.2.1f Events with Increased Relative Risk (RR) and 90% Confidence Interval for Subjects with a History of Asthma: All Settings and All Doses Combined

MAE	Age Group	Number of Participants		Binomial RR (90% CI)
		FluMist n/N	Placebo n/N	
Asthma	18-35 months	8/72	0/33	NA (1.36, NA)
Croup	1-8 years	7/365	0/182	NA (1.29, NA)
Croup	1-17 years	7/552	0/300	NA (1.36, NA)

Table generated by CBER.

URI

In all ages, settings and doses combined, URI events occurred in 8.4% of FluMist and 9% of placebo recipients. In 3 of the 41 separate analyses, a significantly increased risk of URI among FluMist recipients was observed, and for 38 analyses no significant increase or decrease in risk was observed. The three analyses with increased risk of URI are shown in Table 2.2.1g.

Of the total 831 URI events, 811 were evaluated in the clinic only (FluMist, n=527 and placebo, n=284). One placebo recipient was hospitalized for URI (and croup) on Day 4. For FluMist subjects, age 18-35 months for all settings combined, 40% (61/153) of the URI events were reported in the first two weeks post-vaccination. The URI events in the 18-35 month old placebo subjects appeared to be evenly distributed across the 42-day post-vaccination period.

Table 2.2.1g URI Events with Significantly Increased Relative Risk by Age Group and Setting

			Number of Participants* with Events/Number in Age Group		
Age	**Setting**	**Dose**	**FluMist n/N**	**Placebo n/N**	**Binomial Risk (90% CI)**
1-17 years	ED	1	11/6473	0/3216	-- (2.14, NA)
1- 8 years	ED	1	9/3769	0/1869	-- (1.7, NA)
18 – 35 mo	All	Both	153/728	60/369	1.3 (1.01, 1.67)

*Some subjects reported more than one URI event.
NA =not available due to 0 events in placebo subjects
Table generated by CBER

Musculoskeletal pain

In all ages, settings, and doses combined, musculoskeletal pain was reported in 1.7% of FluMist recipients and 1.6% of placebo recipients. For 14 analyses, no significantly increased or decreased risk of musculoskeletal pain was associated with FluMist, and for two analyses, and increased risk was observed. An increased risk was noted in 18-35 month old children following Dose 1, with events occurring in 7/728 FluMist subjects and 0/369 in placebo subjects [RR not calculable, (1.3, NA)] and following both doses combined. The increased risk following Dose 2 reflects the events post-Dose 1, since no additional events were reported following dose 2.

No subjects were hospitalized for musculoskeletal pain. No apparent temporal associations for musculoskeletal pain were observed the 42 days post-FluMist among 18-35 mo old recipients.

Abdominal Pain

In all ages, settings and doses combined, abdominal pain was reported in 0.7% (47/6473) of FluMist recipients and 0.8% (26/3216) of the placebo subjects. Of the 26 analyses performed, for two the RR for abdominal pain was significantly increased, while in two others the RR was significantly decreased. The four analyses with significantly increased or decreased risks are shown in Table 2.2.1h.

Table 2.2.1h Abdominal Pain Events with Significantly Increased or Decreased Relative Risk by Age Group and Setting

			Number of Participants* with Events/Number in Age Group		
Age	**Setting**	**Dose**	**FluMist n/N**	**Placebo n/N**	**Binomial Risk (90% CI)**
1-17 years	ED	Both	14/6473	1/3216	6.94 (1.52, 73.81)
9-17 years	ED	1	7/2704	0/1347	-- (1.28, NA)
1 – 8 years	Clinic	1	8/37569	11/1869	0.36 (0.16, 0.78)
1 – 8 years	All	1	10/3769	12/1869	0.41 (0.20, 0.85)

*One FluMist subject reported two abdominal pain events.
NA = not available due to 0 events in placebo subjects
Table generated by CBER

In the 42-days post-vaccination, no apparent temporal clustering of abdominal pain events was observed for subjects 1-17 years of age in the ED. No specific abdominal disorders were identified for the increased abdominal pain events. Appendicitis/appendiceal abscess (one event in FluMist recipient, though symptoms started prior to vaccination), appendectomy for rule-out appendicitis (one event in a FluMist subject) and acute gastroenteritis (78 events in FluMist and 47 events in placebo subjects) accounted for all of abdominal pain events. No intussusception, intestinal obstruction or mesenteric adenitis events were reported.

Other MAEs
Increased RRs were also noted for some analyses for **otitis media with effusion** (increased only in subjects 1-8 years of age, post-Dose 2)**,** and **adenitis/adenopathy** (no specific region for nodes was identified); however, there was no apparent temporal clustering after vaccination and the RRs for these events were decreased for the other analyses.

MAEs with an Associated Decreased Risk
Of the 21 individual MAEs associated with statistically significant decreased risk in FluMist recipients, 11 were not considered by the sponsor to have a biologically plausible relationship to FluMist. These included attention deficit disorder, behavioral disorder, constipation, contact dermatitis, eczema, gingivitis, gynecologic disorders, migraine, thrush, trauma and well-child care/assurance. The decreased rates observed for the remaining 10 MAEs were considered to have a possible biological plausible association with FluMist (i.e. FluMist may have induced protection against wild type influenza) were abdominal pain, acute gastroenteritis, conjunctivitis, cough, diarrhea, febrile illness, otitis media, pharyngitis, tonsillitis, and viral syndrome.

F. Other Respiratory MAEs of Interest
Pneumonia, bronchitis, bronchiolitis and croup were not associated with a significant increased or decreased risk in FluMist recipients in any of the combined analyses (all age groups, utilization settings, and doses combined) or separate analyses (different age groups, utilization settings or doses).

G. Rare Events Potentially Related to Wild-type Influenza Infection
In association with natural infection with wild type influenza infection, rare adverse events, including neurologic illnesses, have been observed. Because FluMist contains live attenuated influenza viruses, the occurrence of these rare events is theoretically possible and thus, a search for these rare events was included in the safety evaluation of FluMist.

A total of 11 subjects (FluMist n=8 and placebo n=3) reported rare events potentially related to influenza infection. One subject had seizures (FluMist, n=1 on Day 15 in child being followed for a possible seizure disorder); six subjects had febrile seizures (FluMist, n=5 on Days 17, 21, 23, 29 and 35 post-vaccination; placebo, n=1 on day 17), and four subjects had known epilepsy (FluMist, n=2 on days 17 and 25; placebo, n=2 on days 31 and 39 post-vaccination, not reported as new events). None of these events were significantly increased in FluMist recipients compared to placebo, when analyzed separately or combined. No cases of encephalitis, Guillain-Barre Syndrome, Reye Syndrome or any other influenza-associated rare disorders were reported.

AV019 - Conclusions
Of the randomized, controlled trials among children, Study AV019 was the major contributor of subjects to the safety database in this application. As identified in the interim analysis, an increased risk of asthma events was noted in FluMist recipients, ages 18-35 months. This observation was confirmed in the analysis of the finalized dataset. Furthermore, when evaluated in increasing cumulative 6-month intervals starting at age 12 months through 107

months of age, the increased RR for asthma events following Dose 1 reached statistical significance for children 12-59 months, and declined thereafter. No increased risk was observed following Dose 2 in these analyses. However, some children who experienced an AE after Dose 1 did not return for Dose 2, which may affect the observed rate of AEs.

No increased risks of asthma events were observed for subjects age 9 through 17 years. An increase in asthma/wheezing events was not observed in older children, possibly because older children were more likely to have been identified as having asthma and thus, excluded from study participation. This is supported by the data showing that 75% of subjects enrolled in AV019 with a history of asthma were from 1-8 years of age.

Many children with asthma and wheezing were enrolled in AV019, despite entry criteria intended to exclude them (parent/guardian report of a history of asthma or possible asthma history). Of the reports of wheezing post vaccination in children 18-35 months of age, 7 of 16 (44%) occurred among children with a history of wheezing, detected by retrospective examination of medical records. While the sponsor seeks an indication for children who are healthy, the difficulty identifying children with a wheezing history encountered at the HMO conducting the safety study might be encountered in other healthcare settings.

None of the episodes of asthma/RAD in AV019 among children under age 5 years were recorded as "serious" and none resulted in hospitalization. However, it may be expected that timely emergency department and outpatient care of wheezing episodes in children at an efficient HMO may obviate the need for hospitalization. Notably, all of the young children, 18-35 months of age, with post-vaccination wheezing episodes required medical therapy, including beta agonists, and inhaled and/or systemic corticosteroids.

The overall rate of SAEs in this trial of 0.2% is consistent with findings in previous trials of FluMist, though methods for monitoring are different from previous trials, in which generally diary cards were used and subjects were actively monitored for AEs. In this trial, MAEs, including SAEs, were captured through monitoring of the KP database for medical encounters. Therefore, AEs that did not prompt a medical visit were not captured.

Nearly 1500 analyses were performed without statistical adjustment for multiple comparisons. Using a 90% confidence interval for the relative risk to screen for safety outcomes, some MAE rates were increased and others were decreased following FluMist. While it is possible that the association of Flumist administration and increased rates of asthma/wheezing, URI and musculoskeletal pain in 18-35 month old children are spurious findings due to chance alone, these events are observed with wild type influenza infection, and therefore, might occur with the live, attenuated vaccine strains. To gain a better understanding of the true risk of asthma and wheezing in young children, and children with a history of asthma, additional studies would be necessary.

2.2.2. STUDY AV012 (Years 1 and 2): Study of Influenza Virus Vaccine, Trivalent, Types A&B, Live, Cold-Adapted (CAIV-T) in a Community-Based, Non-Randomized, Open-Label Trial in Children to Assess the Safety and Herd Immunity for the Control of Epidemic Influenza.

The primary goal of the study was to assess herd immunity (by assessing the rates of medically attended acute respiratory illnesses, MAARI) afforded by FluMist in communities with vaccinated children compared to communities with unvaccinated children. One of the secondary goals of the study was to evaluate safety, primarily by assessment of SAEs for 42 days post-vaccination. Of note, the data from the communities with unvaccinated children were not available for analysis, and the methods for data analysis were changed from the original design. As discussed with the sponsor prior to submission, the study was not adequately designed to provide data supportive for effectiveness, and only the safety data have been reviewed for the BLA.

2.2.2.1 AV012 - Study Design

This was an open-label, non-randomized clinical trial. Children 18 months through 18 years who resided in the Temple-Belton, TX area or received their primary care at Scott & White Clinic in Temple, TX were eligible. The initial protocol was designed to enroll approximately15, 000 subjects annually during influenza season (August through April) of 3 consecutive years. A subject could be enrolled in Year 1, 2, 3 or any combination of years, and participants received one dose of FluMist for each year they were enrolled.

The primary measure of safety was the occurrence of SAEs within 42 days of vaccination (a secondary goal in the original trial design). Searches of the Scott and White (S&W) database were planned to capture MAARI events for the assessment of herd immunity (the primary objective in the original study design), but during Year 1 sometime after enrollment was completed, capturing MAARI events was added as a secondary assessment of safety.

Scott and White Health Plan (SWHP) is an HMO health insurance plan, and Scott and White Clinic (SWC) is an affiliated clinic. Not all subjects who received care at SWC were insured through SWHP.

The study was designed to assess effectiveness endpoints, i.e. rates of MAARI by comparison with rates among unvaccinated controls selected from HMO populations. However, these planned safety comparisons were not performed in part because data from one control community became inaccessible due to a change in ownership of the HMO. Subsequently, the DSMB recommended utilizing an epidemiologic data analysis technique, using vaccinees as their own controls by comparing the immediate post-vaccination MAARI rates to those during Reference Periods prior to and after vaccination.

The Vaccination Periods were Days 0-14 and Days 0-42 post-vaccination. The Reference Periods for each participant for each year were constructed by combining the pre-vaccination period (1st day of the trial through one day prior to vaccination) and the post-vaccination period (time from Day 15 or Day 43 after vaccination through a defined stop date for each year, as described below) into a single Reference Period. Of note, in the sponsor's comparisons of the rates of MAARI events in the pre-vaccination Reference Period and the post-vaccination Reference Period, statistically significantly lower rates of events were observed in the pre-vaccination period for Year 1 and Year 2 (data not provided here).

Poisson regression was used to calculate relative risk (RR) estimates and confidence intervals (CIs) for the RR of events during the Vaccination Periods compared to the Reference Periods. Age group and season of vaccination were included as co-variates.

Vaccines
A single dose 0.5 ml containing 10^7 TCID each of the 1998-9 vaccine strains A/Beijing/262/95 (H1N1), A/Sydney/05/97 (H3N2), and B/Harbin/7/94 was given for Years 1 and 2, though different lots were used.

Inclusion/Exclusion Criteria Related to Asthma
In the original protocol, subjects were to be excluded if they had asthma; however, not all subjects with a history of asthma, reactive airway disease (RAD) or wheezing were excluded. In Amendment 1 (December 10, 1998), the criteria were revised to permit inclusion of children with "mild wheezing illness" if they were not taking asthma medications (bronchodilators or anti-inflammatory agents) every day or every other day and they had not received emergency treatment/hospitalization for asthma or wheezing in the:

- Previous 12 months for children > 24 months or
- Previous 6 months for children 18-24 months.

Children were to be excluded if they had wheezing episodes in previous two weeks or moderate to severe asthma, the general definition of which was consistent with the 1997 guidelines from the National Heart Lung and Blood Institute.

Safety Monitoring
Parents/guardians were given a 42-day health report card to complete and return, and instructions to call the study site if the subject was hospitalized, developed a serious condition, or became pregnant. An automated phone call was made to the SWHP subjects to remind them to return the completed postcard.

Database searches of Scott & White hospital admissions, hospital observations without admissions, outpatient surgery, and emergency room visits were conducted on a monthly basis for study participants to search for hospitalizations, deaths, pregnancies, MAARI events, and rare events potentially related to wild-type influenza. SAEs occurring after Day 42 were to be collected if they were considered to be related to vaccination. SAEs were defined consistent with 21 CFR 312, as listed in the above report for Study AV019.

2.2.2.2 AV012 – Results
A. Enrollment and Demographics
Year 1: The study period was from August 17, 1998 through January 30, 1999. A total of 4,298 subjects were enrolled, with the median age of 8.3 years. Approximately 24% of the subjects were from 1.4 – 4 years, 31.3% were 5 – 8 years, and 44.6% were 9 -18 years. Females accounted for 49.5%, and most participants were Caucasian (71%), Hispanic (17%), or African American (7%). Of the participants, 53% reported that they were members of SWHP and 79% identified SWC was their primary health care facility. Some subjects were included in both the SWHP dataset and the SWC dataset. Because the 42-day post-vaccination evaluation was completed for the subjects before the onset of influenza in the community, no censoring for onset of influenza season was performed. Therefore, all SWC and SWHP members were considered evaluable for the primary MAARI analysis.
.
Year 2: The study period was from September 13, 1999 through February 20, 2000, and 5251 participants were enrolled. The age and ethnic distributions were similar to Year1. A total of 2102 (40%) subjects were re-vaccinees. Of the 5251 subjects, 71% were identified by the parent/guardian as receiving their healthcare from SWC. Also, 2524 (48%) were identified as

members of SWHP, and 2163 (86%) of the SWHP subjects were evaluable in the primary MAARI analysis, because they were vaccinated before December 4, 1999. The sponsor identified this date as the onset of influenza season.

B. Safety Analyses

Serious Adverse Events

Subjects were considered evaluable for SAE analyses if a 42-day postcard was completed, a successful telephone contact occurred, or if they had SWHP insurance coverage (and thus, their records were available for the database searches). Safety data were not captured in the database searches for subjects (~21% in Year 1; ~29% in Year 2) who were not enrolled in SWHP or followed at SWC.

For all evaluable subjects, the rate of SAEs was 0.2% (eight in 4,131 subjects) in Year 1, and 0.3% (16 in 5,033 subjects) in Year 2 (Table 2.2.3a). These rates are consistent with those reported for other clinical trials, including the rate of 0.2% observed in both the FluMist and placebo groups in AV019.

Year 1

Of the 4,298 enrolled, 4,131 (96.2%) were considered evaluable for SAE analysis. No deaths were reported. Eight SAEs were identified, and none were considered to be definitely, probably or possibly vaccine-related by the investigators. Two of the SAEs occurred in subjects with a history of wheezing; one of these was a groin abscess on Day 25 and one was head trauma and coma from a motor vehicle accident on Day 26.

Year 2

Of the 5251 participants, 5033 (95.8%) were evaluable for SAE analysis. No deaths were reported. In the 5033 subjects, 16 (0.3%) SAEs (all hospitalizations) were identified in 15 subjects and none were considered to be related to study vaccination by the investigators. Nine of the SAEs occurred 21 or more days post-vaccination. Two of the SAEs were related to the respiratory tract; one was RSV pneumonia with a febrile seizure in a 23 mo old on Day 11 post-vaccination and the other was pneumonia in an almost 4 year old, which occurred on Day 44 post-vaccination.

Table 2.2.3a Serious Adverse Events* Reported in FluMist Recipients from Day 0-42 Post-Vaccination in Study AV012 Year 1 and Year 2

Subject Age	Vaccination Date	Days Since Vaccination	Diagnosis
Year 1			
29 mo	11-02-98	25	Groin abscess
7y 4mo	10-20-98	24	Fever and hip pain
6y 11 mo	10-23-98	29	Vomiting
5y 10 mo	10-25-98	26	Fever and vomiting
7y 5 mo	10-31-98	26	Head trauma and coma post-motor vehicle accident
24 mo	11-15-98	33	Croup and stridor
7y 9 mo	11-07-98	21	Aseptic meningitis[1]
16y 8 mo	11-11-98	3	Depression
Year 2			
3y 8mo	10-23-99	2	Pyelonephritis
22 mo	11-06-99	9	Septic hip and UTI due to *E. coli*
23 mo	11-13-99	11	RSV pneumonia and febrile seizure
11y 5 mo	11-05-99	12	Hypospadias repair
17y 11 mo	11-22-99	12	Appendicitis
12y 2 mo	11-11-99 12-06-99	15 40	Depression/Suicide Ideation for both events
9y 7 mo	11-26-99	18	Seizures
11y 6 mo	11-03-00	23	Elective orthopedic surgery/spastic diplegia
10y 3 mo	10-05-99	30	Mononucleosis
23 mo	11-03-99	33	Acute gastroenteritis
4y 1mo	10-02-99	36	Toe amputation
8y 2 mo	9-13-99	38	Dehydration
3 y	10-29-99	38	Gastro-esophageal Reflux
8y 11 mo	10-13-99	40	Schizo-affective Disorder with medication adjustment
3y 11 mo	10-15-99	44	Pneumonia

*****All events were hospitalizations.
[1]This event occurred in a subject who was not a SWHP participant.

C. Results: MAARI Events

Participants were considered evaluable for MAARI analyses if they were insured by SWHP or they received their primary care at SWC, i.e., their records were available for the database searches.

MAARI events in participants in the "Wheezing Subset" in SWHP and SWC were also analyzed. Subjects identified in a retrospective review as having a parent-provided history of wheezing and/or had a pre-vaccine ICD-9 code for wheezing upon database searches were considered eligible for analysis in the wheezing subset.

Selected respiratory events were assessed separately from the overall MAARI analysis. These events included acute otitis media (AOM)/sinusitis, pneumonia, bronchitis, bronchiolitis, croup, and asthma/wheezing.

Year 1: MAARI Events

In Year 1, the pre-vaccination Reference Period was from August 17, 1998 until the day of vaccination and the post-vaccination Reference Periods were from Day 15 or Day 43 after vaccination to January 30, 1999.

No significantly increased RR for MAARI events or selected respiratory events were observed in either Vaccination Period (Days 0-14 or Days 0-42) compared to the Reference Period for the 2,225 SWHP participants. Also, no significant increases in RR for MAARI events or in the selected respiratory events were observed for the Vaccination Periods compared to the Reference Period for the 3,406 SWC participants.

Year 1 - MAARI Events in the Wheezing Subset

In the wheezing subset of 309 SWHP participants, no significant increase in RR of MAARI events or any of the selected respiratory events was observed in either Vaccination Period (Days 0-14 or Days 0-42) compared to the Reference Period.

In the wheezing subset of 453 subjects using SWC for their healthcare, a significant increase in RR of MAARI in the Day 0-14 Vaccination Period (RR = 1.34, LB of 90% CI = 1.06) was seen; however, no increase in RR for the selected respiratory events was observed. In the Day 0-42 Vaccination Period, no increase in RR of MAARI events or selected individual respiratory events was observed in the SWC wheezing subset.

Year 2: MAARI Events

In Year 2, the pre-vaccination Reference Period was from 9-13-99 until the day of vaccination, and the post-vaccination Reference Period was the time post-vaccination from Day 15 or Day 43 through 12-4-99 for the primary MAARI analysis (before influenza activity in the community) and through 2-10-00 for the Year 2 overall MAARI analysis (end of the study period for Year 2). The pre- and post-vaccination Reference Periods were combined into a single Reference Period for the MAARI analyses.

A total of 2163 of the 2524 (85.7%) SWHP participants were vaccinated before 12-4-99. For these subjects, no significant increases in the RR for MAARI events in the Day 0 -14 Vaccination Period compared to the Reference Period were observed. However, in the Day 0 - 42 Vaccination Period, a significant increase in the RR of MAARI events (RR = 1.17, 90% CI 1.04,1.31) compared to the Reference Period was seen, though no increases in the RR for the selected respiratory events were observed. Results are shown on Table 2.2.2a.

Similar MAARI analyses were performed for the 3,427 SWC participants vaccinated before 12-4-99. For SWC participants, there was a significant increase in RR of MAARI events for the Vaccination Periods Day 0-14 (RR = 1.12, 90% CI 1.0-1.25) and Day 0-42 (RR = 1.13, 90%CI: 1.03-1.24) compared to the Reference Period. A significantly increased RR was also observed for the selected event of asthma/wheezing for Days 0-42 (RR = 1.83, 90% CI: 1.26, 2.67).

Year 2: MAARI Events in the Wheezing Subset

There were 388 subjects with SWHP and 545 subjects who used SWC for their care, with a history of asthma/wheezing, who were vaccinated before 12-4-99. For these subjects, no significant increases in RR of MAARI events for the Day 0-14 or Day 0-42 Vaccination Periods compared to the Reference Period were observed.

Year 2: MAARI Events in Re-Vaccinees

MAARI events were assessed in repeat vaccinees (subjects immunized in Year 1 and Year 2) enrolled in SWHP. The primary analysis of MAARI events was performed for 1054 subjects immunized before 12-4-99. No significant increases in RR of MAARI events were observed for the Day 0-14 or Day 0-42 Vaccination Periods compared to the Reference Period, as shown on Table 2.2.2a.

Year 2: MAARI Events Over the Year 2 Complete Study Period

Across the entire study period (9-13-99 through 2-10-00) for the SHWP and SWC participants, no increases in the RR for MAARI in any of the analyses were observed for the Day 0-14 Vaccination Period compared to the Reference Period. For subjects receiving their healthcare at SWC, statistically significant increases in RRs were noted for the Days 0-42 Vaccination Period for MAARI events (RR = 1.08, 90%CI 1.01-1.16) and for the selected event of asthma/wheezing (RR = 1.45, 90%CI: 1.1-1.91), Table 2.2.2a.

Table 2.2.2a Study AV012 – Year 2 Overall Summary of Relative Risks (RRs) and Confidence Intervals (CIs) for MAARI Events Prior to Influenza Greatest Intensity (December 4, 1999) and the Total Safety Analysis Period (February 2, 2000) by Population and Vaccination Period

Population	Days	Prior to Influenza Season			Total Safety Period		
		Poisson Analysis			Poisson Analysis		
		N	RR	90%CI	N	RR	90%CI
SWHP	**0-14**	2163	1.08	0.94-1.25	2524	1.03	0.91-1.17
	0-42	2163	1.17	1.04-1.31	2524	1.08	0.99-1.18
SWHP Wheezing	**0-14**	388	1.12	0.86-1.46	443	1.14	0.91-1.44
	0-42	388	1.17	0.94-1.45	443	1.15	0.98-1.36
SWC	**0-14**	3247	1.12	1.00-1.25	3748	1.07	0.97-1.19
	0-42	3247	1.13	1.03-1.24	3748	1.08	1.01-1.16
SWC Wheezing	**0-14**	545	1.14	0.91-1.42	622	1.16	0.95-1.41
	0-42	545	1.08	0.90-1.30	622	1.10	0.95-1.41
SWHP Re-vaccinees	**0-14**	1054	1.00	0.80-1.24			
	0-42	1054	1.14	0.96-1.36			
SWHP Wheezing Re-vaccinees	**0-14**	168	0.99	0.66-1.48			
	0-42	168	1.29	0.94-1.79			

The Relative Risk (RR) was considered significantly increased if the lower bound of the 90% CI was 1.0 or greater. The RR and CI were adjusted for age group and season. Shading indicates that analyses were not performed. SWHP=Participants with Scott and White Health Plan. SWC=Participants receiving care at Scott and White Clinic. Table from MedImmune – Jan 2002 CR Responses, Vol. 12, page 59.

AV012 – Results: Rare Events Potentially Related to Influenza Infection

Rare events that have been associated with natural wild-type influenza virus infection were ascertained, even if they did not meet the definition of an SAE. These events included encephalopathy, encephalitis, Guillain-Barré syndrome, myocarditis, and pericarditis. The database searches for these rare events were performed at the end of each year of the study. None of these rare events were reported during the 42-day post-vaccination monitoring period in Year 1 or Year 2.

Other CNS events such as seizures and meningitis, identified in this trial, are discussed below in Section 2.3.4.

Comparative Analyses of Asthma/Wheezing Events in AV012 and AV019
The sponsor performed a comparison of asthma rates in the 28 days post-vaccination in AV012 and AV019 for children from 18 months through 83 months of age, using only Dose 1 data from AV019. No comparisons for children over 83 months of age were provided.

The rates of asthma/RAD were approximately 0.5-1.5% (5-17 per 1000 person-months) among all FluMist recipients for both studies. For FluMist recipients with a history of asthma/RAD, rates of asthma/RAD events [2-7.5% (20-80 per 1000 person-months)] were higher than those for all FluMist subjects. Rates of asthma/RAD in FluMist subjects with a history of asthma/RAD were similar for AV019 and AV012-Year 1, but were 3 to 5% higher for AV012-Year 2.

While AV012 did not include a randomized control group, it is of interest to note that the rates of asthma in this study were similar to those in FluMist recipients in Study AV019. In AV012, the RR for asthma was not increased in Year 1 in any of the analysis, but was significantly increased in Year 2 for some analyses, including in the Day 0-42 Vaccination Period for SWC and SWHP participants. Differences for the rates of MAARI were observed between Year 1 and Year 2 of AV012, which may in part be due to the difference in timing of vaccination of the subjects, since all participants completed the 42-day post-vaccination period before onset of influenza in Year 1, compared to 86% did in Year2.

Several issues must be considered in performing a comparison of events in Studies AV012 and AV019. Most importantly, the designs of the two trials were different, with AV012 being open-labeled, which may have influenced participants' behavior in seeking medical care. The monitoring in the both trials included searches of the databases at the respective HMOs, though the methods used were different. The diagnostic coding was different for the two trials; in AV019, coded terms for MAE from clinic, ED and hospitalizations were searched and for AV012, pre-specified terms for MAARI were searched. Subjects with known asthma/wheezing were excluded in AV019 (likely most relevant for excluding older children with known asthma) while enrollment of children with known mild wheezing was permitted in AV012. Although the age groups overlapped, the demographic characteristics differed, suggesting that the populations may not have been comparable. Finally, these trials were performed in different geographic locations during different calendar years and thus, the wild-type influenza epidemiology, and possibly for other respiratory viruses, may have differed. Interestingly even with these differences, the overall rates of asthma events (~1%) in the FluMist recipients, as well as the rates of SAEs at 0.2% were comparable in both trials.

AV012 – Conclusions
CBER viewed the safety analyses performed in Study AV012 and conclusions drawn from these analyses of limited value for the following reasons:

1) The study was not randomized, controlled, or blinded for safety assessments;
2) The lack of an appropriate control group limits the usefulness of statistical comparisons;
3) Analysis of MAARI as a safety endpoint was not prospectively defined;
4) The epidemiologic method used for the analyses has most often been applied to acute events, with short duration and no associated seasonality and thus, may not be valid for events that are highly correlated with seasonality or are chronic in nature (such as asthma); and
5) Combining the pre and post Reference Periods for the analysis of MAARI events may not be justified due to statistically significant differences in event rates observed between the two periods.

Although a randomized comparator group is not available for AV012, some observations were similar to those in AV019 and the relatively large number of subjects vaccinated with Flumist provides useful data for estimating rates of SAEs associated with vaccine administration. The reported rates of SAEs were low and other rare events potentially associated with influenza infection were not observed during the 42-day post vaccination period.

2.2.3 Study Wyeth DP145-500: A Randomized, Double-Blind Trial of Safety, Transmissibility, and Phenotypic and Genotypic Stability of Influenza Virus Vaccine, Trivalent, Types A and B, Live, Cold-Adapted (CAIV-T) in Children Who Attend Day Care.

Study Design

This was a randomized double-blind trial performed in Finland in healthy children, 8 to 36 months of age who attended day care. The study objectives were to assess the safety, tolerability and transmissibility of CAIV-T compared to placebo. Approximately 200 children were randomized 1:1, CAIV-T to placebo. As per the original protocol, the children had to be part of a contact group of at least 6 children (later decreased to 4) in the playroom enrolled into the study with at least one child randomized to receive CAIV-T. Eligible children had to attend day care at least 3 times per week for at least 4 hours per day.

In the original study design, the primary endpoint was the proportion of placebo recipients from whom any of the vaccine strains were isolated. Subsequently, the sponsor stated that a better end point might be the probability that a vaccinated subject would infect an unvaccinated subject, since each placebo subject may be exposed to a number of vaccinated subjects. Thus, in the August 2002 CR responses, the sponsor implemented a new analysis approach, the Reed-Frost Model. This chain binomial model estimates the probability of a subject becoming infected when exposed to infected subjects (i) as $[1 – (1 – p)^i]$, where p is the probability of a subject becoming infected from a single infected subject. With this method, the number of FluMist vaccinees that transmitted vaccine viruses was estimated, in contrast to assessing the number of placebo subjects infected, as planned in the original design.

Vaccines and Schedule

The FluMist vaccine used for this study was the1998-9, which included A/Beijing/262/95 (H1N1), A/Sydney/05/97 (H3N2) and B/Harbin/7/94-like, and each 0.5 ml dose contained 10^7 $TCID_{50}$ of each strain of virus in normal allantoic fluid (NAF). The placebo was NAF.

Approximately 42 days after the first dose of study vaccine, an optional dose of CAIV-T was offered to participants in an open-labeled fashion.

Monitoring

Solicited reactogenicity events (RE) were captured for 21 days post-vaccination (for Dose 1) and for 10 days after the optional vaccine (2^{nd} dose), and serious adverse events (SAEs) were evaluated for 42 days after each vaccination.

Nasal swabs were obtained for culture just prior to vaccination on Day 0, Day 1 and, thereafter, on 3 alternating days per week (e.g. Mon, Weds, Fri) during the 21-day post-vaccination monitoring period. Vaccine viruses isolated from participants were typed (A or B) and subtyped (A/H3N2 or A/H1N1). The isolates were further analyzed for any alteration of their phenotype [cold adapted (*ca)* or temperature-sensitive (*ts)* abilities], and the genotypes of a subset of isolates were characterized to assess the stability of the 6:2 reassortant genome. Initial cultures were performed at the Turku laboratory in Finland and sent to MedImmune for confirmation and further analyses.

D145-P500 - Results

A total of 197 children were enrolled (98 FluMist recipients, 99 placebo recipients) at 51 daycare centers. Of the 197 enrolled, 133 received the second dose of study vaccine (69 from FluMist group and 74 from prior placebo group).

Demographic characteristics were similar among the first dose FluMist and placebo groups with respect to gender (55% male, overall), ethnicity (97% Caucasian, overall), age (mean 26.4 months, median 27.8 months, overall) and body temperature at the time of dosing.

No study subject was in a room with less than 5 children, but not all of the children were necessarily study participants. Non-participants who became ill during the study had the opportunity to have a nasal swab obtained, though only 3 non-participants had nasal cultures performed. The time of exposure of vaccinees to the placebo recipients was not reported.

The primary analyses of viral transmission were performed on the *evaluable transmission population*. This population consisted of the 57 placebo recipients with 21 days of follow-up (f/u) and nasal swabs at intervals $\leq$ 4 days. These subjects also had to be in a playroom with at least 4 children in the study and at least 1 CAIV-T recipient, and were 8 to 36 months of age. Forty-two placebo subjects were excluded from the evaluable population because of protocol deviations. Among the 42 subjects excluded, the most common reasons for exclusion were that the subject had fewer than four study subjects in the playroom (n=21) or the subject had less than 21 days of f/u (n=13). A summary of protocol deviations in both study groups is provided in the CSR.

A secondary analysis of viral transmission was carried out on the *all-available transmission population*. This included the 99 placebo recipients, since each had at least one nasal swab evaluated post-dose 1. However, six placebo subjects had no exposure to a FluMist recipient, and the sponsor revised this population to exclude these six subjects, leaving 93 subjects in the *all-available transmission* population.

The analyses of vaccine virus shedding were carried out on the *all-available shedding* population, which consisted of the 197 children enrolled, as each of these children had at least one nasal swab obtained.

As noted above, with the August 2002 CR responses, re-analyses of the data for the *all-available* population were performed using the Reed-Frost Method, and these results are provided.

Vaccine shedding among CAIV-T (FluMist) recipients:

A summary of the shedding results is shown in Table 2.2.3a. Receipt of FluMist led to shedding of at least one strain in 80% of vaccinees. Of the FluMist recipients, 43 (44%) shed type A vaccine virus (H3N2 = 12 and H1N1=31), and 72 (74%) shed type B vaccine virus. Six of the 43 FluMist subjects shed a type A virus whose subtype could not be identified. Six subjects shed both type A strains and six subjects shed all 3 types (H3N2, H1N1 and B). Thirteen FluMist recipients shed viral strains (6 type A plus 7 type B) that could not be identified for subtype and/or phenotype. No FluMist recipients were identified as shedding wild-type influenza. Of note, A/H1N1 did not circulate during the study period.

The mean duration of shedding for A/H3N2 was 8.5 days (range 3-17 days), for A/H1N1 was 5.3 days (range 1-21 days) and for type B was 7.0 days (range 1-15 days). However, subjects did not have cultures obtained daily, so a definitive duration of shedding cannot be determined.

Table 2.2.3a. Number of FluMist and Placebo Participants In D145-P500 with Influenza Virus Shedding and Characteristics of Shed Viruses

	Treatment Group	
Influenza Strain Shed	**FluMist, N=98 n(%)**	**Placebo, N=99 n(%)**
Any Strain	78 (80)	7 (7)
Days of Shedding		
Mean (SD)	7.6 (3.4)	9.7 (7.5)
Median	8.0	8.0
Range (Days)	1-21	0-21
Any A Strain (A/H1N1 or A/H3N2)	43 (44)	6 (6)
Days of Shedding		
Mean (SD)	6.2 (4.6)	8.8 (7.8)
Median	6	7
Range	1-21	0-21
Vaccine Strain	37(38)	0
Wild type Influenza	0 (0)	2 (2)
Unidentified	6 (6)	4 (4)
A/H1N1 Strain	31 (32)	0 (0)
Days of Shedding		
Mean (SD)	5.3 (5.0)	0
Median	3	0
Range	1-21	0
Vaccine Strain	31 (32)	0
Wild type Influenza	0 (0)	0
Unidentified	ND	ND
A/H3N2 Strain	12 (12)	2 (2)
Days of Shedding		
Mean (SD)	8.5 (3.7)	12 (12.7)
Median	8	12
Range	3-17	3-21
Vaccine Strain	12	0
Wild type Influenza	0(0)	2 (2) [b]
Unidentified	12 (12)	ND
B Strain	72 (74)	1 (1) [a]
Days of Shedding		
Mean (SD)	7.0 (2.7)	15
Median	8	15
Range	1-15	-- [a]
Vaccine Strain	65 (66)	1 (1) [a]
Wild type Influenza	0 (0)	0
Unidentified	7 (7)	0

[a] One placebo subject shed type B vaccine strain on Day 15 only, as a result of transmission.
[b] Strain A/H3N2 was isolated from two placebo recipients; this strain was circulating in the community at the time of the study.
ND = Not able to determine.
Table generated by CBER.

Transmission

Influenza virus was recovered from seven placebo recipients, six of whom were included in the *evaluable transmission* population. One subject, who shed type A, was excluded from the analysis because there was > 4 day interval between nasal swabs. Vaccine virus was not recovered in the swabs from the three non-participants who had nasal cultures obtained.

One placebo recipient shed vaccine virus, type B/Ann Arbor only on Day 15, which was identified by genotype and phenotype analysis. This subject also had cultures obtained on Days 0, 1, 3, 6, 8, 10, 13, 17, 20 and 21, all of which were negative. Two FluMist recipients and three placebo recipients were enrolled in this subject's contact group. Both of the CAIV-T recipients were vaccinated two days after the placebo subject and both CAIV-T recipients shed type B, which ended on Day 8 post-vaccination. Therefore, the transmitted virus was detected 13 days post-vaccination with respect to the date of FluMist administration and five days after the last detectable shedding from either FluMist recipient (i.e. Day 8).

Of the 7 placebo subjects who shed influenza viruses, 6 subjects had 9 positive cultures for type A influenza. Two strains were identified as wild type virus A/H3N2 strains, which were isolated from two placebo subjects on two different days (four isolates). Four subjects shed five type A strains that could not be identified by subtype or sequence. Based upon the timing of viral isolation and the known exposure to a FluMist recipient, it is likely that two of these isolates were wild type (cultures were positive on Day 0); however, for the other three isolates, vaccine strain virus cannot be ruled out.

According to the sponsor's analysis plan, only isolates that could be identified definitively as vaccine strains were to be included in the analysis. With the original analysis plan, the per protocol rate of transmission was 1.75% (1/57), with an upper bound of the 95% CI of 8.05%. Similar analyses of the *all-available transmission population* (n=93, excluding 6 children without contact with a FluMist recipient) yielded an estimated transmission rate of 1.01% (1/93) with an upper bound of the 95% CI of 4.70%.

CBER generated an estimate of transmission using the sponsor's original analysis approach including all of the unidentified type A strains as possible vaccine strains, i.e. n=5 subjects with possible transmitted influenza viruses (one subject with type B plus 4 subjects with unidentified type A vaccine strains). Assuming that the unidentified isolates were vaccine virus, the rate of transmission was 5% (5 of 93 placebo subjects) with an upper bound of 9.58%.

Using the Reed-Frost Model, the various estimates of transmission (with only the single vaccine strain-infected placebo subject included) are shown in Table 2.2.3b.

Table 2.2.3b Probability of Transmission of Vaccine Strain Virus Using Reed-Frost Model in Study D45-P500

Population	n	Probability of Transmission(p)[a]	95% CI
Per protocol	57	0.0090	0, 0.027
Per protocol + subjects with > 4 day swab interval	70	0.0073	0, 0.021
All evaluable subjects	93 [b]	0.0058	0, 0.017

[a] Based on the Reed-Frost model for infection

[b] Excludes six subjects in a playgroup with no CAIV-T recipients.

Table from MedImmune, August 2002 CR response, #-39, Volume 2, page 1.

In the Reed-Frost analysis using subjects in the all available population (n=93) and including the four placebo subjects with viruses that could not be identified, the probability of transmission is 0.0236 with upper bound of the 95% CI of 0.0459.

Phenotype and Genotype Results

In this trial, all of the isolates from placebo recipients and a subset of those from FluMist recipients were genotyped using consensus method. The following criteria were used to select the isolates that were sequenced:

- Immunoperoxidase staining of the inoculated cultures indicating that the sample contained a single virus subtype,
- The sample had adequate virus content (i.e, approximately 100-1000 infectious foci),
- Samples originating from swabs taken at later times post-vaccination were chosen to maximize the chances of detecting nucleotide misincorporations during replication in the vaccine recipient.

The consensus genomic sequences of individual clinical isolates were compared directly to the consensus sequence of the relevant virus harvest (VH) used to make the trivalent formulation evaluated in Study D145-P500. This formulation was comprised of the following viral harvests: CAE058 [A/Beijing/262/95 (H1N1)] + CAE059 [A/Sydney/5/97 (H3N2)] + CAE042 [B/Ann Arbor/1/94 (B/ Harbin-like)]. The results for the placebo subjects are shown in Table 2.2.3c

The B/Ann Arbor/1/94 strain isolated from the infected placebo subject was found to have three sequence changes (nucleotide difference for the isolate as compared to the VH – see Table 2.2.3c and Table 1 in Appendix 4.1). Similarly, changes were identified in viruses shed by vaccine recipients. Fifty-five of 237 potential isolates were evaluated for nucleotide changes compared to the vaccine consensus sequence (21 of 39 influenza A/H1N1 isolates, 12 of 18 influenza A/H3N2 isolates, none of 16 influenza A un-typed isolates and 22 of 164 type B isolates, including the vaccine strain isolated from the placebo recipient). Nucleotide changes were identified in most of them, and some isolates exhibited nucleotide changes in as many as 5 of the 6 genes contributed by the attenuating donor strain. The minority of viruses tested (five A/H1N1 strains, one A/H3N2 and five type B strains) showed no change compared to the consensus (Appendix 4.1).

Table 2.2.3c. Finnish Daycare Safety and Horizontal Transmissibility Study, D145-P500: Placebo Recipients Shedding Influenza Virus

Subject No.	Accession No.	Day Post-Vaccination	Virus Type Recovered[a]	Subtype[b]	Consensus Sequence[c]
1001	P02940	15	Type A	No Result[d]	No Result[d]
1026	P00781	0	Type A	No Result[d]	No Result[d]
	P01266	6	Type A	No Result[d]	No Result[d]
1040	P00762	0	Type A	No Result[d]	No Result[d]
1028	P01459	8	Type A	No Result[d]	No Result
1076	P01685	1	Type A	H3N2	wt Panama
	P01690	3		H3N2	wt Panama
1090	P02075	20	Type A	H3N2	wt Panama
	P01850	21		H3N2	wt Panama
1197	P01193	15	Type B	Vaccine (B/Ann Arbor)	[e]Sequence Changes HA (457) G to A M (718) G to A NS (753) A to G

[a]Virus culture performed by Turku Laboratory.
[b]Virus subtyping performed by Aviron Laboratory.
[c]Sequencing performed by Wyeth laboratory.
[d]No Result = could not be subtyped; no viable virus present.
[e]Sequence Changes = nucleotide differences when clinical isolate is compared to the relevant VH.
Table from MedImmune, August 2002 CR response #40, Volume 3, page 29.

Nucleotide changes were not at random positions, but represented either selection of an underlying non-dominant sequence or the occurrence of new mutations during replication of the vaccine virus in nasal tissues. Since H1N1 and H3N2 influenza A subtype viruses used in the live attenuated vaccine have the same internal donor gene source, sequence changes noted for the H1N1 and H3N2 subtype strains may be combined. For influenza A vaccine viruses, repeated changes in a specific nucleotide occurred in PB1, PB2, NP and M genes. For influenza B viruses, repeated changes in a specific nucleotide occurred in the M gene.

None of the nucleotide changes documented was found in a position known from published literature to be critical for attenuation (Herlocher et al., Virus Research, 1996, 42:11-25). In all instances, cold adaptation (ability to replicate at 25 C) and temperature sensitivity (inability to replicate at 39^{o}C for influenza A and 37^{o}C for influenza B), two of the three important phenotypic markers of the live vaccine strains, were retained. However, documentation that the attenuation phenotype was retained by the isolates as demonstrated by specific *in vivo* tests (e.g. inoculation of ferrets) was not provided.

Safety

Reactogenicity results within 10 days of 1st study dose were similar among FluMist and placebo/NAF recipients. The subject who received influenza type B virus as a result of transmission, reported a runny nose on days 8-18, cough on days 8 and 9, and irritability on days 0, 14, and 17.

D145-P500 Conclusions

This study was performed to provide estimates of shedding and vaccine virus transmission among young daycare attendees. Because of several limitations, including study design issues (time of exposure is not known and the intermittent culturing), small size, and protocol deviations, these results may not be generalized to other settings. With acknowledgment of the limitations, the data showed that viral shedding did occur following receipt of FluMist in this age group (in the range of 80%), and persisted in some vaccinees for at least 21 days, the last day

cultures were obtained. Additionally, transmission of vaccine virus also occurred, though only a crude rate can be estimated. The one placebo recipient infected with vaccine strain type B had symptoms consistent with the reactogenicity profile observed in FluMist vaccinees.

This small trial demonstrates that shed vaccine viruses have a high probability of mutation or selection of genetic sequences during replication in vaccine recipients. Nucleotide changes, which were identified in most of the vaccine viruses shed, were not random, since the same nucleotide changes were found in multiple viruses examined. The B/Ann Arbo/1/94 vaccine strain recovered from the placebo subject had three identified nucleotide changes, though there was no loss of the attenuated phenotype based on the clinical experience of the single subject. The clinical significance of the observed nucleotide changes is not known.

2.3 Specific Adverse Events – Review Across Studies

Because of ongoing safety concerns at the time of the July 2001 VRBPAC Meeting, review of several adverse events, including asthma, pneumonia, conjunctivitis and abdominal pain across all studies was performed by the sponsor. The following techniques were used for these analyses:

Events were collected across the 20 completed clinical studies submitted to the BLA (summarized in Table 1.1.1). Fourteen of the studies were randomized, double-blind, and placebo-controlled, and three of these trials (Studies AV006, AV009, and AV019) were pivotal safety studies. Two of these studies were conducted in healthy children, Study AV006 in 1,602 children 15 to 71 months of age (a two year trial) and Study AV019 in 9,733 children 1-17 years of age. Study AV009, was conducted in 4,561 healthy adults. In addition to the 14 double-blind, placebo-controlled studies, six non-placebo-controlled trials were also included in the review. Because of the limitations in performing analyses across studies, this discussion will primarily focus upon the results from the randomized, placebo-controlled trials.

Events were identified from five possible data sources from the 20 studies including, adverse events (AEs), serious adverse events (SAEs), illness evaluations for influenza surveillance, health care utilization database search, and comments noted on case report forms (CRFs). Events that occurred within the reactogenicity event (RE) monitoring period (primarily 7 days for adults and 10 days for children), medically attended event (MAE) period from Day 0-42, or the SAE monitoring period (generally Day 0-28 for adults and Day 0-42 for children) were analyzed. Events occurring after the 42-day monitoring period were not included in these safety analyses. The events were summarized for Days 0-21 (21 Day Summary Period) and Days 0-28/42 (28/42 Day Summary Period). For some analyses, the results for the two Summary Periods were similar, and only the Day 28/42 data are provided in this discussion.

Statistical analyses comparing incidence rates between the FluMist and placebo groups were performed for the three pivotal, randomized, placebo-controlled studies and age-specific analyses for the two pivotal trials in children were also performed. Relative risks (RR, the incidence rate in FluMist divided by incidence rate in placebo) and two-sided 90% confidence intervals (CIs), adjusted for follow-up time, are presented for these studies.

2.3.1 Asthma, Wheezing, and Shortness of Breath (SOB)

Because an increase in the relative risk (RR) for asthma was identified in 18-35 month old FluMist recipients in the Interim Analysis of AV019, asthma/wheezing events in all of the studies in the BLA were reviewed. Study AV019 was the major contributor of children for the analysis for the randomized, placebo-controlled trials. Of the 4,839 children < 9 years of age who received FluMist, 3,791 (78%) were from AV019; the others were from AV006.

Cases of asthma/RAD and cases of wheezing/SOB were identified and combined in one category of asthma/RAD/wheezing/SOB for analysis to help account for the overlap in the use of these terms.

Results

Approximately 82-88% of asthma/RAD/wheezing/SOB events and 74-83% of asthma/RAD events across all 20 studies in both treatment groups occurred in children 1 to <9 years of age; however, children in this age group comprised approximately 50% of the total study population. The asthma/RAD/wheezing/SOB events and asthma/RAD events for FluMist recipients were distributed throughout the 42-day post-vaccination period with no evidence of temporal clustering.

SAEs

Four SAEs in three participants were identified as asthma/RAD/wheezing/SOB events in the 20 completed studies. One FluMist recipient with a history of asthma in Study AV006 Year Two was hospitalized for status asthmaticus that occurred eight days following receipt of his third dose of FluMist. One 69 year old FluMist recipient in Study AV008 with a history of history of heart disease and multiple chronic illnesses was hospitalized on Day 16 post-vaccination for 10 days for hypoxemia secondary to congestive heart failure and pleural effusion. One placebo recipient with a history of asthma in Study AV002 was hospitalized twice for RAD. This participant's initial one-day hospitalization was four days following receipt of placebo, and a second one-day hospitalization occurred 33 days later.

Relative Risks in the Placebo-Controlled Trials

Asthma/RAD

In the three pivotal studies, the risk of asthma/RAD in FluMist recipients compared with placebo recipients for the 28/42 Day Summary Period was not significantly increased. When able to be computed, the point estimates for relative risk ranged from 0 -1.44 (Table 2.3.1a).

In the other 11 randomized, placebo-controlled studies, too few events occurred to enable computation of relative risk for most studies. For the three studies where relative risk could be computed (Studies AV002, AV007, and AV010), no significantly increased risks were observed.

Table 2. 3.1a Number of Asthma Events, Incidence Rates, and Relative Risks for All Participants by Study for the Three Pivotal Trials (AV006, AV009 and AV019)

Study	Dose	28/42 Day Summary Period		
		FluMist n/N (Rate)	Placebo n/N (Rate)	Relative Risk (90% CI)
AV006 Year One	1	3/1070 (1.99)	0/532 (0.00)	NA (0.43, NA)
	2	4/854 (3.32)	2/418 (3.39)	0.98 (0.23, 5.15)
AV006 Year Two	1	6/917 (4.63)	5/441 (8.03)	0.58 (0.21, 1.65)
AV009	1	0/3041 (0.00)	1/1520 (0.69)	0 (0.00, 4.50)
AV019	1	<9 years: 23/3791 (5.22)	8/1894 (3.63)	1.44 (0.74, 2.94)
		?9 years: 13/2704 (3.40)	9/1347 (4.73)	0.72 (0.35, 1.51)
	2	<9 years: 27/3242 (5.90)	14/1600 (6.19)	0.95 (0.56, 1.66)
		?9 years: 0/1 (0.00)	--	NA (NA)

Note: Excludes follow-up visits and duplicate events occurring on the same day.
Rates provided per 1000 person-months.
Table adapted from MedImmune, August 2002 CR response #43.

Asthma/RAD/Wheezing/SOB

In the three pivotal studies, the RR of asthma/RAD/wheezing/SOB in FluMist recipients compared with placebo recipients for the 28/42 Day Summary Period was not significantly increased. The point estimates for relative risk ranged from 0.51-1.47. The risk of asthma/RAD/wheezing/SOB in FluMist recipients was significantly decreased compared with placebo recipients in participants in Study AV006 Year Two, i.e., the upper bound of the 90% CI was less than one (RR: 0.51; 90% CI: 0.28, 0.94). Because of the number of analyses performed without adjustment for multiple comparisons, it was expected that some significant outcomes, increased or decreased, were observed due to chance alone.

In the other 11 randomized, placebo-controlled studies, the RR could be computed for four studies (Studies DMID #98-005, AV002, AV002-2, AV007). No significantly increased risks were seen.

Relative Risks for Children < 9 Years (Asthma History-Positive and History-Negative)

A similar approach to that presented for Study AV019, in which event rates and relative risks were examined by cumulative increments of 6 months of age, was utilized for analysis of the two placebo-controlled trials that enrolled FluMist-*naïve* children, i.e. AV006 - Year 1 and AV019. Cumulative analyses are presented through 71 months of age for AV006 – Year 1 and for children through 107 months of age for AV019.

Asthma/RAD

In AV006, in Year 1 three events, all in FluMist subjects occurred after Dose 1 and six events (4 FluMist and 2 placebo) were reported after Dose 2. Because of the small number of events, no definitive conclusions can be made.

In AV019, 3,721 children < 71 months (compared to 1,602 enrolled in AV006) were enrolled. In AV019, 31 asthma/RAD events occurred after Dose 1 (23 in FluMist and 8 in placebo for event rates of 5.22 and 3.63 per 1000 person-months, respectively). After Dose 2, 41 events occurred, 27 in FluMist and 14 in placebo with event rates of 5.9 and 6.19 respectively. Looking at increasing 6 months increments following Dose 1, RR point estimates initially increased as

older children were included, peaked in the 12-59 month age cohort (RR = 3.53, 90% CI 1.1, 15.66), and declined thereafter (see Table 2.2.1d). After Dose 2, the RR point estimates showed a similar pattern of increasing risk with inclusion of older children, but the observed increase was not statistically significantly. As noted above, some children who experienced an AE after Dose 1 did not return for Dose 2, which may impact upon the number of AEs observed after Dose 2.

Asthma/RAD/Wheezing/SOB

In AV006, 40 events occurred after Dose 1 (27 in FluMist and 13 placebo) and 32 events occurred after Dose 2 (24 in FluMist and 8 in placebo). No significant increase in RR was observed for any of the cumulative age groups, and no pattern for increasing RR with inclusion of older children was noted.

In AV019, 55 asthma/RAD/wheezing/SOB events occurred after Dose 1: 37 in FluMist and 18 in placebo subjects with event rates of 8.4 and 8.17 per 1000 person-months, respectively. There were 69 events after Dose 2: 45 in FluMist and 24 in placebo with event rates of 9.83 and 10.62, respectively. No statistically significant increase in RR was observed after either dose. The peak RR was observed in children 12-53 months of age after Dose 1 (RR=2.19, 90% CI: 0.9, 6.0) and after Dose 2 (RR=1.21, 90% CI: 0.69, 2.17).

AV019 and AV006

Increased risk in FluMist recipients for asthma/RAD events was seen only in Study AV019, and not in Study AV006. One potential explanation for these findings is that Study AV019 enrolled approximately 2.5 times as many children in the comparable age group (?71 months) as were enrolled in Study AV006, and therefore, had higher power to detect a treatment effect. Furthermore, the methods for collecting outcomes in the two studies was markedly different: adverse events in Study AV006 were identified by adverse event case report forms (CRFs), comment CRFs, and illness forms, while in Study AV019, medically attended events were collected from HMO utilization databases.

Asthma Summary for Participants in Randomized, Placebo-Controlled Trials

In the three pivotal placebo-controlled trials (AV006, AV019 and AV009), no significant increases in RR for asthma/RAD or asthma/RAD/wheezing/SOB were seen in the analyses for FluMist recipients < 9 years, 9-17 years or 18-64 years of age. However in the analysis performed by age group in six-month increments, a significant increase was seen for asthma/RAD in FluMist subjects 12-59 months of age after Dose 1 in AV019. This significantly increased RR was not observed for this age group for the analysis of all events combined, asthma/RAD/wheezing/SOB.

Asthma History-positive Subjects in Placebo-Controlled Trials
Relative Risk

In the pivotal, placebo-controlled trials (Studies AV006, AV009, and AV019), no significant increase in risk for asthma/RAD or asthma/RAD/wheezing/SOB outcomes was seen in FluMist recipients compared to placebo recipients with a prior history of asthma, RAD, or wheezing for the age groups of <9 years of age, 9 to 17 years of age, or 18 to 64 years of age (Table 2.3.1b). In an analysis of children 12 to 107 months of age examined by cumulative 6-month increments, no significantly increased risk was seen for asthma/RAD or asthma/RAD/wheezing/SOB.

Table 2.3.1b Number of Asthma/Wheezing/SOB Events, Incidence Rates, and Relative Risks for History Positive Participants by Study for the Three Pivotal Trials (AV006, AV009 and AV019)

Study	Dose	28/42 Day Summary Period		
		FluMist n/N (Rate)	Placebo n/N (Rate)	Relative Risk (90% CI)
AV006 Year One	1	3/20 (106.5)	2/9 (157.3)	0.68 (0.14, 3.82)
	2	2/18 (78.65)	0/7 (0.00)	NA (0.18, NA)
AV006 Year Two	1	5/29 (122.0)	2/11 (128.7)	0.95 (0.24, 4.77)
AV009	1	2/25 (83.97)	1/13 (80.74)	1.04 (12, 15.08)
AV019	1	<9 years: 21/1022 (17.67)	9/511 (15.31)	1.15 (0.60, 2.29)
		?9 years: 6/481 (8.83)	7/258 (19.21)	0.46 (0.18, 1.18)
	2	<9 years: 27/878 (21.77)	15/437 (24.30)	0.90 (0.53, 1.55)

Table adapted from MedImmune, August 2002 CR response #49.

AV010

This study enrolled a total of 48 subjects (24 FluMist and 24 placebo) 9 –17 years of age with moderate to severe asthma. Of the 24 FluMist recipients, two had asthma exacerbations within 28 days post-vaccination, and one subject had an exacerbation on Day 32 post-vaccination; no exacerbations were observed for the placebo subjects. However, because of the small sample size, the study did not have adequate power to rule out differences in the occurrence of asthma exacerbation between the two treatment groups.

Summary for History-positive Subjects

In the analyses of asthma/RAD/wheezing/SOB and asthma/RAD, the event rates in subjects with a history of asthma, RAD, or wheezing in randomized, placebo-controlled trials were similar in FluMist and placebo recipients, and were higher than the rates observed in subjects without a history of asthma or wheezing. Because children with wheezing are more likely to have a wheezing event (as evidenced by an increase rate of events post-vaccination in both the FluMist and placebo recipients) and the placebo was NAF, the vaccine-attributable risk (due to the vaccine vehicle of NAF, influenza strains, or other vaccine components) is difficult to discern.

Asthma Events - Overall Conclusions

This across study analysis does not provide significant additional information regarding the risks of asthma/RAD events for children beyond the information provided from Study AV019, in part because participants in AV019 comprised the majority of children in these analyses.

Statistically significant increased RRs for asthma/RAD for FluMist recipients were found in:

- Study AV019, for children 18-35 months of age (for three analyses per planned study analyses),
- Study AV019, for children 12-53 months of age for both doses combined (post-hoc analysis for CSR), and
- Study AV019, for children12-59 months of age after Dose 1 (cumulative age group by 6 month intervals, performed for CR request). For this group, the RR=3.53 (90% CI: 1.1, 15.66).

In analyses by age group in six-month increments, a pattern of increasing risk with the inclusion of progressively older children through age 59 months, with a subsequent decline thereafter,

was observed. No temporal clustering in the 42 days post-vaccination was observed. A history of asthma or wheezing may be an important factor for risk of asthma/wheezing events in the 42 days post-vaccination. With the identified significantly increased risk of asthma/RAD for young children < 60 months regardless of wheezing history, and the increased risk for subjects with a history of asthma/RAD, the safety concerns for use of FluMist in these populations persist. To gain a better understanding of the true risk of asthma and wheezing in young children and individuals with a history of asthma, additional studies would be necessary.

2.3.2 Pneumonia, Bronchitis and Bronchiolitis

At the time of the July 2001 VRBPAC, the safety database, including identification of all pneumonia, bronchitis and bronchiolitis events, was not complete and thus, CBER had not completed the review. At that time, there were concerns about a possible increased rate of pneumonia events following receipt of FluMist. An analysis of pneumonia events across all studies was performed by the sponsor, and no increased risk for pneumonia events was observed.

Pneumonia SAEs

Two pneumonia events in FluMist recipients led to hospitalization and were reported as SAEs. One subject in AV012 was hospitalized with culture-positive RSV pneumonitis with an associated febrile seizure. One subject in AV006 – Year 2 was hospitalized on Day 8 post-vaccination for status asthmaticus with increase in perihilar markings on chest radiograph (CXR).

Relative Risk for Pneumonia Events in Three Pivotal Placebo-Controlled Trials

The RRs of pneumonia in FluMist recipients compared with placebo recipients in the three pivotal studies (Table 2.7.1) were not significantly increased in the analyses for either the 21 Day Summary Period or the 28/42 Day Summary Periods.

Table 2.3.2 Relative Risks of Pneumonia Events in the Three Pivotal Studies (AV006, AV009 and AV019)

Study	21 Day Summary Period		28/42 Day Summary Period	
	Relative Risk	(90% CI)	Relative Risk	(90% CI)
AV006[a] Year One, Dose One	2.49	(0.45, 9.32)	3.48	(0.69, 9.25)
AV006 Year One, Dose Two	0	(0.00, 4.41)	0.65	(0.18, 2.59)
AV006 Year Two	NA	(0.62, NA)	2.4	(0.44, 8.36)
AV009 18-64 Years	NA	(0.06, NA)	NA	(0.06, NA)
AV019 Dose One, <9 Years	0.33	(0.11, 0.99)	0.56	(0.26, 1.21)
AV019 Dose Two, <9 Years	0.74	(0.31, 1.85)	0.76	(0.40, 1.47)
AV019 ?9 Years	NA	(0.43, NA)	NA	(0.43, NA)

Note: Confidence intervals (CI) computed using Mid-p exact binomial method. A significantly increased risk is defined by the lower bound of the CI ?1.0.

NA = not available due to 0 events occurring in placebo recipients.

[a]Children were 15 to 71 months of age at initial enrollment.

Table adapted from MedImmune, January 2002 CR response, #45

Summary of Pneumonia, Bronchitis and Bronchiolitis

In summary, from the data analyses within and across clinical studies in healthy children and healthy adults, receipt of FluMist was not associated with an increased risk of pneumonia. Additionally, similar analyses performed for bronchitis and bronchiolitis did not identify an increased risk for these events following receipt of FluMist.

2.3.3 Abdominal Pain

An increase in abdominal pain was observed in AV006 -Year 1 in FluMist recipients compared to placebo subjects. Because abdominal pain may be observed with influenza infection, analysis of this event was performed.

In the three pivotal studies, most abdominal pain events (59%) of events in FluMist recipients and 49% in placebo recipients occurred in the first seven days after dosing. Two abdominal pain events were reported as SAEs in FluMist recipients; abdominal pain/rule-out appendicitis (9 days post-dose 1 in AV006 – Year 1) and gynecologic pain (10 days post-dose 1 in Study AV019).

Relative Risk for Abdominal Pain

The RR and CI for the abdominal pain events in the 21 Day and 28/42 Day Summary Periods in participants in the three pivotal studies are presented in Table 2.3.3a. There was a significant increase in the RR of abdominal pain events for FluMist recipients in Study AV006 Year- 1 after the first dose in the 21 Day Summary Period (RR 3.65, 90% CI: 1.40, 11.58) and in the 28/42 Day Summary Period (RR 2.69, 90% CI: 1.24, 6.44). However, after the second dose in Study AV006 Year One and revaccination in Year Two, no significant increases in abdominal pain events was observed in either the 21 Day or 28/42 Day summary period.

In Study AV019, as discussed above, significantly increased risks in FluMist recipients was found in children 1-17 years of age following both doses combined in the ED and in children 9-17 years of age following a single dose in the ED. There were also two analyses that showed significantly decreased risks in abdominal pain for FluMist recipients (in children 1-8 years of age following the first dose of FluMist in all settings and in the clinic setting, Table 2.2.1h

In adults in Study AV009, a significant decreased risk of abdominal pain (RR 0.55, 90% CI: 0.33, 0.94) following receipt of FluMist compared to placebo was observed.

For the two pivotal studies in children, a significant increase in risk was noted in one of the age-specific analyses in FluMist recipients, children 25-48 months of age in Study AV006 (Table 2.3.3a). This increase was not seen for this same age group, 25-48 months of age, in Study AV019, in which the relative risk was 0.52 (90% CI: 0.08, 3.34) in the 21 Day Summary Period and 0.26 (90% CI: 0.05, 1.13) in the 28/42 Day Summary Period. The monitoring of events was performed differently in AV019; most notably, only medically attended abdominal pain events were captured.

Table 2.3.3a Relative Risks of Abdominal Pain in Pivotal Studies (AV006, AV009 and AV019)

Protocol	21 Day Summary Period		28/42 Day Summary Period	
	Relative Risk	(90% CI)	Relative Risk	(90% CI)
AV006[a]				
Year One, Dose One	3.65	(1.40, 11.58)	2.69	(1.24, 6.44)
Year One, Dose Two	1.10	(0.41, 3.24)	1.35	(0.52, 3.86)
Year Two, Dose One	1.20	(0.46, 3.49)	0.88	(0.38, 2.14)
AV009				
18-64 Years	0.55	(0.33, 0.94)	0.55	(0.33, 0.94)
AV019				
Dose One, <9 Years	0.5	(0.17, 1.49)	0.42	(0.20, 0.85)
Dose Two, <9 Years	0.82	(0.24, 3.11)	1.60	(0.64, 4.52)
?9 Years	1.00	(0.41, 2.62)	1.08	(0.61, 1.96)

Note: Confidence intervals (CI) computed using Mid-p exact binomial method. A significantly increased risk is defined by the lower bound of the CI >1.0. NA = not available due to 0 events occurring in placebo recipients.
[a]Children were 15 to 71 months of age at initial enrollment.
Table from MedImmune, January 2002 CR response, #48

Summary of Abdominal Pain Events

The relative risk for abdominal pain was increased in children, 25-48 months of age after Dose 1 of FluMist in Study AV006. An increase in abdominal pain events was not seen in this age group in Study AV019. However, AV019 captured only medically attended events, and thus, the data are not comparable. Abdominal pain following FluMist is biologically plausible, but may not be severe enough for parent to seek medical care for their children.

2.3.4 CNS Events

Central nervous system (CNS) events, such as seizures, encephalitis, meningitis, and encephalopathy, have been reported in association with wild type influenza infection. Therefore, a search for CNS events across all studies was performed. All reported CNS events and confirmed CNS events (confirmation based upon review of medical records) during the 21 Day and 28/42 Day Summary Periods were analyzed. Follow-up visits and "pre-scheduled" routine visits for CNS disorders were not included in the analyses.

Confirmed CNS Events in the Placebo-Controlled Trials

For the confirmed events analyses in the three pivotal randomized (2:1), placebo-controlled studies (AV006, AV009 and AV019) in the 28/42 Day Summary Period, 13 confirmed CNS events were identified: eight after 15,618 (0.05%) FluMist doses, and five after 7,752 (0.06%) placebo doses. Sixty-two percent of the 13 confirmed events occurred in children ≤ 71 months of age. Seven of the eight (88%) FluMist and three of the five (60%) placebo recipients were female. None of the 13 confirmed events in the three pivotal placebo-controlled trials was reported as an SAE (one event in AV007 was reported as an SAE, described below). In review of temporal clustering of CNS events post-vaccination, four of the eight (50%) events in the FluMist subjects occurred from Day 15 through 21 post-vaccination. A summary of the confirmed events is provided in Table 2.3.4b.

In the other 11, randomized, placebo-controlled studies in the 28/42 Day Summary Period, two CNS events after 16,686 FluMist doses (0.12%) and no events in the placebo group were reported. In the six non-placebo-controlled studies, 15 confirmed CNS events were reported in the 28/42 Day Summary Period.

Table 2.3.4b. Confirmed New CNS Events Observed in the 28/42 Day Safety Period Post-Vaccination in the Three Pivotal Trials (AV006, AV019 and AV009).

Study	Event	Age	Treatment Group	Dose	Day of Event Post-vaccination
AV006 - Year 1	Stiff neck associated with Sore throat	4y	FluMist	1	9
	Febrile seizure	3y	Placebo	2	10
AV006 – Year 2	No events				
AV019	Syncope/LOC* (History of Seizures)	2y	FluMist	1	15
	Syncope/LOC*	8y	Placebo	2	12
	Febrile Seizure and Otitis media	1y	FluMist	2	29
	Febrile Seizure	4y	Placebo	2	17
	Staring spells	7y	Placebo	2	42
	Fever/ acute seizure (History of seizures)	7y	FluMist	1	23
	Febrile seizure and Otitis media	1y	FluMist	1	17
	Acute event possible seizure with fever and URI (History of Seizures)	1y	FluMist	2	21
	Syncope/LOC	1y	FluMist	1	17
AV009	Neck pain and Delirium	25 y	Placebo	1	2
	Confusion and Blurred vision	28 y	FluMist	1	0

*LOC – loss of consciousness
Table generated by CBER

Number of CNS Events

In all of 20 trials, 34 CNS events were identified in the all event analysis within the 28/42 Day Summary Period; 16 in randomized, placebo-controlled studies [11 in FluMist recipients after 17,304 FluMist doses (0.04%) and five in placebo recipients after 8,477 placebo doses (0.06%)] and 18 events in non-controlled studies. In the all event analysis, four events in FluMist recipients required hospitalization or were reported as an SAE. These events included head injury and seizure on Day 23 post-vaccination in a 2-year-old female (Study AV007), confusion associated with hypoxia and heart failure on Day 16 in a 69 year old (Study AV008), aseptic meningitis on Day 21 in a 7-year-old female (AV012 – Year 1), and a febrile seizure associated with culture-positive RSV pneumonia on Day 11 in 19 month old female (AV012 – Year 2). No hospitalizations were reported for CNS events in placebo subjects.

Relative Risks

The RR and 90% CIs for the CNS events in both the 21 Day and 28/42 Day Summary Periods in participants in the three pivotal studies are presented in Table 2.3.4c. In these three studies, no significantly increased risk for CNS events in FluMist recipients for either the 21 or the 28/42 Day Summary Period was observed.

Table 2.3.4c Relative Risks of Central Nervous System Events in Pivotal Studies

Study	21-Day Summary Period		28/42 Day Summary Period	
	Relative Risk	(90% CI)	Relative Risk	(90% CI)
AV006[a]				
Year One, Dose One	NA	(0.06, NA)	NA	(0.06, NA)
Year One, Dose Two	0	(0.00, 4.41)	0	(0.00, 4.41)
Year Two	NA	NA	NA	NA
AV009				
18-64 Years	0.5	(0.03, 9.50)	0.5	(0.03, 9.50)
AV019				
Dose One, <9 Years	NA	(0.43, NA)	NA	(0.86, NA)
Dose Two, <9 Years	0.25	(0.02, 2.12)	0.33	(0.06, 1.61)
?9 Years	NA	NA	NA	NA

Note: Confidence intervals (CI) computed using Mid-p exact binomial method. A significantly increased risk is defined by the lower bound of the CI >1.
NA = not available due to 0 events occurring in placebo recipients.
[a] Children were 15 to 71 months of age at initial enrollment.
Table adapted from MedImmune, Jan 2002 CR response, #49.

Confirmed CNS Events in the All 20 Completed Trials

Across all studies, there were 30 confirmed CNS events in 28 subjects within the 28/42 Day Summary Period. Of these 30 events, 17 seizure events in 15 subjects were reported. Two subjects had two seizure events each; for one of these subjects, the seizure events occurred on Day 31 and on Day 39 after FluMist with a characteristic EEG for benign simple partial seizures. Another subject with a prior history of neonatal meningitis, static encephalopathy, seizures, residual visual impairment, and developmental delay had two seizure events on the same day (coded as “febrile seizure” and “seizure” on Day 13 after FluMist). A synopsis of the children with seizure events in AV012 is provided on Table 2.3.4c and for children in the placebo-controlled trials in Table 2.3.4d.

Among the 17 seizure events, seven were ”febrile seizures”, nine were “other seizures” and one was coded as “seizure with fever.” The event coded as “seizure and fever” occurred on Day 23 post-vaccination in a FluMist recipient with a history of recurrent seizures. Five of the seven febrile seizures occurred in the placebo-controlled trials (three in FluMist recipients on Days 17, 21 and 29 and two in placebo recipients on Days 10 and 17). The other two febrile seizures occurred in FluMist recipients in on Day 11 (febrile seizure associated with culture-positive RSV pneumonia) and on Day 13 (discussed in paragraph above) following vaccination in AV012. The nine seizure events coded as “other seizures” occurred post-vaccination on Days 5, 13, 16, 22, 23, 26, 27, 31, and 39. One of these seizure events occurred following a head injury in a FluMist recipient 23 days after vaccination; this subject had a prior history of seizures. The other eight seizure events occurred in Study AV012. These events were distributed across the 42-day post-vaccination period without apparent temporal clustering.

Table 2.3.4c Participants With Seizure Events in Days 0–42 in Study AV012

Study Number	Sex	Age in (Years)	Treatment Group	Vaccination One Date	Vaccination Two Date	Event Start Date	Event	Days Since Last Vaccination	Prior[a] History of Seizure	Routine Follow-up Visit
AV012-1	Female	6	FluMist	31-Aug-98		31-Aug-98	CONVULSIONS OT	0	Yes	Yes
						21-Sep-98	CONVULSIONS OT	21		Yes
						28-Sep-98	CONVULSIONS OT	28		Yes
						05-Oct-98	CONVULSIONS OT	35		Yes
AV012-1	Female	13	FluMist	02-Oct-98		14-Oct-98	CONVULSIONS OT	12	Yes	No
AV012-1	Male	10	FluMist	07-Oct-98		02-Nov-98	CONVULSIONS OT	26	Yes	Yes
AV012-1	Female	6	FluMist	14-Oct-98		14-Oct-98	CONVULSIONS OT	0	Yes	Yes
AV012-1	Female	3	FluMist	21-Oct-98		26-Oct-98	CONVULSIONS	5	No	Unk
AV012-1	Male	16	FluMist	24-Oct-98		20-Nov-98	CONVULSIONS OT	27	No	Unk
AV012-1	Male	7	FluMist	31-Oct-98		26-Nov-98	CONVULSIONS OT	26	No	No
AV012-1	Male	9	FluMist	07-Nov-98		15-Dec-98	CONVULSIONS OT	38	No	No
AV012-1	Female	8	FluMist	07-Nov-98		25-Nov-98	CONVULSIONS OT	18	Yes	Yes
AV012-1	Female	6	FluMist	07-Nov-98		23-Nov-98	CONVULSIONS OT	16	Yes	No
						24-Nov-98	CONVULSIONS OT	17		Yes
AV012-1	Male	12	FluMist	25-Nov-98		25-Nov-98	FEBRILE CONVULSIONS	0	Yes	Yes
AV012-1	Female	10	FluMist	09-Dec-98		09-Dec-98	CONVULSIONS OT	0	Yes	Yes
AV012-2	Male	4	FluMist	09-Oct-99		27-Oct-99	CONVULSIONS OT	18	Yes	Yes
AV012-2	Female	3	FluMist	13-Oct-99		03-Nov-99	CONVULSIONS OT	21	Yes	No
AV012-2	Female	11	FluMist	21-Oct-99		21-Oct-99	CONVULSIONS OT	0	Yes	Yes
						12-Nov-99	CONVULSIONS OT	22		Unk
AV012-2	Female	18	FluMist	26-Oct-99		03-Dec-99	CONVULSIONS OT	38	Yes	Yes
AV012-2	Male	12	FluMist	27-Oct-99		11-Nov-99	CONVULSIONS OT	15	No	No
AV012-2	Male	9	FluMist	30-Oct-99		30-Nov-99	CONVULSIONS OT	31	No	Yes
						08-Dec-99	CONVULSIONS OT	39		Unk
AV012-2	Male	3	FluMist	29-Oct-99		06-Dec-99	CONVULSIONS OT	38	Yes	Yes
AV012-2	Male	9	FluMist	13-Nov-99		26-Nov-99	CONVULSIONS OT	13	Yes	No
							FEBRILE CONVULSIONS			
						29-Nov-99	CONVULSIONS OT	16		Yes
AV012-2	Female	1	FluMist	13-Nov-99		24-Nov-99	CONVULSIONS OT	11	No	No
							FEBRILE CONVULSIONS			
						25-Nov-99	CONVULSIONS OT	12		Yes
AV012-2	Male	9	FluMist	15-Nov-99		15-Nov-99	CONVULSIONS OT	0	Yes	No
AV012-2	Male	12	FluMist	20-Nov-99		22-Nov-99	CONVULSIONS OT	2	No	Yes

[a] Yes indicates a prior history of seizures or a work-up for possible seizures that pre-dated the coded event date.

Table adapted MedImmune, August 2002 CR response #35 and November 2002 correspondence.

Table 2.3.4d Placebo Controlled Trials with Participants With Seizure Events in Days 0–42 in Children (AV006, AV007 and AV019)

Study Number	Sex	Age in (Years)	Treatment Group	Vaccination One Date	Vaccination Two Date	Event Start Date	Event	Days Since Last Vaccination	Prior[a] History of Seizure	Routine Follow-up Visit
AV006	Female	3	Placebo	03-Oct-96	05-Dec-96	15-Dec-96	FEBRILE SEIZURE	10	No	No
AV007	Female	2	FluMist	07-Jul-97	13-Aug-97	05-Sep-97	CONVULSION SECONDARY TO HEAD INJURY	23	Yes	No
AV019	Female	2.5	FluMist	11-29-00	Not given	12-14-00	Seizures Syncope/LOC	15	Yes	N/A
AV019	Female	1.3	FluMist	11-13-00	1-15-01	12-12-00 12-13-00	Seizures, Febrile Seizures, Febrile	29 30	No	N/A
AV019	Male	4	Placebo	11-06-00	12-11-00	12-28-00	Seizures, Febrile	17	No	N/A
AV019	Female	7.6	FluMist	11-29-00	---	12-22-00	Seizures, Febrile	23	Yes	N/A
AV019	Female	1.6	FluMist	10-31-00	11-28-00	11-17-00	Seizures, Febrile	17	Yes	N/A
AV019	Female	1.7	FluMist	11-08-00	12-08-00	12-29-00	Seizures, Febrile	21	Yes	N/A
AV019	Female	1.7	FluMist	11-17-00	12-20-00	12-12-00	Epilepsy	25	Yes	Yes
AV019	Male	6.6	Placebo	11-30-00	1-11-01	1-08-00	Epilepsy	39	Yes	Yes
AV019	Female	11.3	Placebo	11-10-00	---	12-11-00	Epilepsy	31	Yes	Yes
AV019	Male	15.9	FluMist	12-11-00	---	12-28-00	Epilepsy	17	Yes	Yes

[a] Yes indicates a prior history of seizures or a workup for possible seizures that predated the coded event date.

N/A = not available

This table does not include one subject (#131142) in Study AV019 who received the coded diagnosis of “seizure, febrile” in error.

Table adapted form MedImmune, August 2002 Cr response #49 and November correspondence.

CNS Events Other Than Seizures

Thirteen CNS events other than seizures occurred within the 28/42 Day Summary Period. These included stiff neck or neck pain in four subjects (Days 2, 3, 5, and 9) without evidence of meningitis, disorientation or confusion in three subjects (Days 0, 0, and 16), loss of consciousness or syncope in four subjects (Days 12, 15, 17, and 38), staring spells in one subject and aseptic meningitis in one subject. The meningitis event occurred on Day 21 following FluMist vaccination in AV012 (in a non-SWHP participant) and was reported to be consistent with an enteroviral infection; however, no laboratory confirmation was provided.

No events of Reye's syndrome, Guillain-Barre syndrome, encephalitis, or new onset encephalopathy were reported following receipt of FluMist.

Summary

Overall, the rate of CNS events, including seizures, following receipt of FluMist was low. In the two randomized, placebo-controlled studies in children (Studies AV006 and AV019), CNS events including seizures were not associated with a statistically significant increased risk for FluMist recipients analyzed by age group or dose compared to placebo recipients. In addition, the overall binomial rate for confirmed CNS events was similar for FluMist and placebo recipients in Study AV019 (0.09% for both treatment groups). In AV019, four of the eight seizure events in FluMist recipients occurred between Days 15 and 21, though the overall number of events is too small to make any assessments of temporal clustering.

Most of the events coded as febrile seizures occurred in young children, less than 72 months of age, which is consistent with the recognized epidemiology of febrile seizures. Among children five years of age and older, the occurrence of febrile seizures post-vaccination is expected to be infrequent. Further characterization of febrile seizures, as well as other CNS events, especially in young children should be incorporated into future clinical trials with FluMist.

2. 4 Data for Re-Vaccination of Older Children and Adults

No data are available for immunogenicity, efficacy or effectiveness for re-vaccination with FluMist in older children (10-17 years) or adults (18-64 years).

For safety data for repeat vaccination in older children and teens, the sponsor cites experience of subjects 1.4 – 18 years of age in AV012. In that trial, 2101 subjects received a dose of FluMist in Year 1 and again in Year 2. Of the 2101, 1054 (459 who were 10-18 years of age) were available for database searches for MAARI events in the 42 days post-vaccination. In Year 2 of the trial for the 1054 subjects, the RR (90% CI) for MAARI in the 42 days post-vaccination was 1.14 (0.96-1.36). For the 459 S&W subjects $\geq$ 10 years of age, there was no statistically significant increase in RR for MAARI in the 14-day post-vaccination period compared to the reference period. However, the RR for MAARI events in the Day 0-42 post-vaccination period compared to the reference period, was significantly increased, RR = 1.5 (1.04 – 2.15, 90%CI).

Efficacy and safety data for re-vaccination of younger children were available for AV006. The efficacy of FluMist in re-vaccinees in AV006 -Year 2 against all community-acquired strains (type A/H3N2 and B) was 87.1% (95% CI: 77.7, 92.6). The post-vaccination safety profile for the FluMist recipients of all age groups in Year 2 was not remarkably different from that observed in Year 1. Five to eight months later, 222 of these children participated in Study AV011, where they received a challenge dose of the monovalent A/H1N1 vaccine strain. In AV011, the safety profiles in prior FluMist and prior placebo subjects were similar, and protection from shedding of the vaccine strain was demonstrated, which the sponsor considered a surrogate of efficacy. These subjects were invited to receive a dose of FluMist for a third year

in Study AV015, which evaluated safety but not efficacy. There was no increase in the post-vaccination reactogenicity events reported for the repeat vaccinees in AV006 or AV015.

2.5 Concomitant Immunization

No data for safety, immunogenicity or efficacy for FluMist given concomitantly with any other vaccinations have been submitted to the BLA.

The sponsor has initiated a trial, AV018, evaluating concomitant use of FluMist with MMR? and VARIVAX? in 12-18 month old children.

2.6 Shedding and Transmission of Vaccine Virus

In four clinical trials, routine post-vaccination cultures were performed to assess the shedding of vaccine strains. These trials include 1) AV002/002-2, a Phase II trial performed to assess the safety and immunogenicty of a two-dose regimen in adults and children, 2) AR001, a Phase I/II trial comparing the safety and immunogenicity of classical formulation of FluMist with a recombinant preparation, 3) AV011, evaluation of a challenge dose of monovalent strain A/H1N1 in participants (FluMist and placebo) from AV006 and 4) Wyeth-sponsored D145-P500, designed to assess the shedding and transmission of FluMist in daycare attendees.

Additionally, though obtaining cultures in the first 10 days post-vaccination was not generally a part of routine procedures, cultures from ill subjects (FluMist and placebo recipients) in this time period were performed for a few of subjects. These data are also discussed below.

2.6.1 Shedding

Routine Cultures Obtained from Days 0-10

For all studies combined, the total number of recipients of the classical formulation of FluMist, who were cultured and the percent who were culture-positive (~34%) are shown in Table 2.6.1a, and similar data, presented by study, are in Table 2.6.1b.

Table 2.6.1a Summary of Shedding Influenza Cultures Days 0–10, All Studies Combined for Participants Who Received the Classical Formulation of FluMist

Total Participants with Cultures	Shed n (%)
569	196 (34.45)

Table from MedImmune, August 2002 CR response, #48.

Table 2.6.1b Summary of Shedding Influenza Cultures Days 0–10, by Study for Participants Who Received the Classical Formulation of FluMist

Study	Total Participants with Cultures	Shed n (%)
AR001 (Classical)	15	3 (20.00)
AV002/AV002-2	234	90 (38.46)
AV011[a]	222	25 (11.26)
D145P500	98	79 (79.59)

[a]In AV011, FluMist participants were challenged with a monovalent vaccine strain, A/H1N1, approximately 5-8 months after receiving their second or third dose of CAIV-T in Year 2 of AV006.
Table from MedImmune, August 2002 CR response #48

The timing of cultures post-vaccination for each study and the number of strains recovered are shown in Table 2.6.1c.

Table 2.6.1c Timing of Influenza Cultures and Number of Strains Recovered During Days 0–10 by Study

FluMist or Monovalent CAIV Recipients			
Study	**Timing of Cultures (Days Post-Vaccination)**	**Strain Recovered**	**Total Number of Strains**
AR001 (Classical)	3	Influenza A	1
		Influenza B	2
AV002 & AV002-2	1-2, 3-5, 7-10	H1N1	10
		H3N2	71
		B	89
AV011[a]	1, 2, 3, 4	H1N1	35
D145-P500	0, 1, and 3/week[b]	H1N1	39
		H3N2	18
		Influenza A	16
		B	164

[a]Monovalent A/H1N1 vaccine strain recipients.
[b]Three times per week on alternating days (e.g. – Monday, Wednesday, and Friday).
Table from MedImmune, August CR response #48

In Study D145-P500, routine cultures were obtained through Day 21 post-vaccination. The mean duration of shedding (from day of vaccination until last day of detectable shedding) for all vaccine strains in CAIV-T recipients was estimated to be 7.6 days (range 0-21 days). Subjects did not have cultures obtained daily, so the definitive duration of shedding cannot be determined. However, vaccine virus shedding was detectable through Day 21 post-vaccination.

Cultures Obtained from FluMist and Placebo Subjects with Illness, Days 0-10

A total of 49 illness cultures obtained from Days 0-10 had growth identified as "Any Flu," and a summary of these illness cultures is presented in Table 2.6.1d. Forty of the 290 (~13.8%) cultures obtained from FluMist recipients were identified as positive for "any flu." All 20 isolates tested were shown to be vaccine strains (Table 2.7.2).

Table 2.6.1d Summary of Illness Cultures Days 0–10, All Studies Combined

FluMist		Placebo[a]	
Total Participants with Cultures	**Any Flu n (%)**	**Total Participants with Cultures**	**Any Flu n (%)**
265	36 (13.58)	100	9 (9.00)
Total Cultures	**Any Flu n (%)**	**Total Cultures**	**Any Flu n (%)**
290	40 (13.79)	112	9 (8.04)

[a]Placebo includes one participant who received TIV in Study AV003.
Table from MedImmune, August 2002 CR response #48

Of the 20 strains that were tested and identified as vaccine strains, 17 of these were from the Houston site from Year 1 of AV006. All 17 subjects reported one or more reactogencity event at the time shedding of the vaccine strains was detected.

2. 6.2 Transmission of Vaccine Virus

Transmission of FluMist was assessed in Study D145-P500, which is discussed above. Although this trial did not clearly specify the extent of the exposure that placebo subjects had with FluMist recipients, transmission was observed. Specifically, isolation of type B vaccine strain from a placebo recipient with exposure to a FluMist recipient who was shedding the type B strain was documented. Four additional isolates in that study could not be definitively identified as vaccine or wild type strain, but vaccine strain could not be definitely ruled out for at least two of the four indeterminant strains.

Summary

Transmission of CAIV strains did occur, but the exact rate cannot be determined with the current dataset. As discussed above, at least one third of CAIV-T recipients (and up to 80% in D145-P500) shed vaccine virus following FluMist, and thus, detecting transmission is not surprising. The placebo subject infected with type B vaccine virus had a similar safety profile as primary recipients of FluMist. However with the small sample size, it is not known if shedding and subsequent transmission of CAIV-T vaccine strains poses any risks to secondary contacts, such as individuals with certain underlying medical conditions (e.g. immunodeficiency or reactive airway disease).

Additionally, insufficient data are available to assess if viruses transmitted human-to-human will retain their attenuated phenotypes. Only one transmitted vaccine strain was documented. Although nucleotide changes were identified for the transmitted type B influenza virus, the strain maintained its cold adapted and temperature sensitive phenotypic markers by *in vitro* testing, but no data from testing (i.e. ferret model) to assess retention of the attenuation phenotype were provided.

2.7 Genotype and Phenotype Stability

2.7.1 Genotype and Phenotype of Isolates Obtained for Routine Cultures

Genotyping and phenotyping were performed for some isolates in AV002/002-2 and D145-P500, and the tested strains are shown in Table 2.7.1. No reversions of a vaccine strain from cold-adapted (*ca*) and temperature-sensitive (*ts*) to wild type were observed.

Table 2.7.1 Phenotype and Genotype of Influenza Cultures Recovered During Days 0–10 by Study for Participants Who Received the Classical Formulation of FluMist

Study	Strain Recovered	Number of Strains						
		ts[a]	Non *ts*[b]	Vaccine Phenotype[c]	Non-Vaccine Phenotype[b,c]	ND[d]	NT[e]	Genotyped[f]
AV002 & AV002-2	H1N1 (N=10)	1	1	3	1	4	--	6
	H3N2 (N=71)	37	--	10	--	24	--	11
	B (N=89)	30	--	10	--	49	--	11
D145-P500	H1N1 (N=39)	--	--	39	--	--	--	18
	H3N2 (N=18)	--	--	18	--	--	--	10
	Influenza A (N=16)	--	--	--	--	16	--	-
	B (N=164)	--	--	68	--	19	77	22

[a] *ts* =Temperature Sensitive
[b] In Studies AV002 and AV002-2 wild-type H1N1 influenza circulated in the U.S. during the routine post-vaccination period when cultures were obtained.
[c] Includes four additional phenotype testing results that were not presented in Table 32 of the CSR for Studies AV002 and AV002-2.
[d] ND = Test attempted, but phenotype not determined.
[e] NT = Not Tested
[f] All maintained 6:2 reassortant, except for two wild-type H1N1 and three not determined (one H1N1, one H3N2, and one B in Studies AV002 and AV002-2).
Table from MedImmune, August 2002 CR response #48

2.7.2 Genotype and Phenotype of Isolates Obtained for Illness Evaluations

Of the 49 illness cultures identified with growth of "Any Flu," 21 isolates were phenotyped (n=19 from AV006 Year One and n=2 from Study AV015). A summary of illness cultures and phenotyping/genotyping status for isolates available form all studies combined is shown in Table 2.7.2. Genotyping was performed for 18 of 19 isolates from FluMist recipients in Study AV006 Year One and both of the isolates from AV015. All 20 isolates obtained for illness evaluations proved to be vaccine strain (one type A/H1N1, seven type A/H3N2 and 12 type B). None of the vaccine strains recovered were reported to have an altered phenotype (*ca* and *ts*).

Additionally, 69 cultures were obtained from placebo recipients in AV006-Year One (data not shown). Of these 69, six type A/H3N2 isolates were recovered that could not be phenotyped. No additional information for these six isolates is provided. Since several participants in AV006 were from families with both FluMist and placebo recipients and type A/H3N2 was circulating in the U.S. during the time of the trial, it is difficult to deduce the phenotype of the unidentified isolates.

Table 2.7.2 Phenotype and Genotype of Influenza Cultures from Classical FluMist Recipients with Illness During Days 0–10, by Study

Study	FluMist					
	Total Cultures Taken	Total Influenza Positive n (%)	Influenza Strain Recovered	Vaccine Phenotype[a]	Phenotype Not Tested	Genotype as 6:2
AR001 (Classical)	2	0 (0.0)	-	-	-	-
AV001	6	3 (50.0)	Influenza A	-	2	-
			Influenza B	-	2	-
AV002 & AV002-2	64	16 (25.0)	Influenza A	-	12	-
			Influenza B	-	5	-
AV003	1	0 (0.0)	-	-	-	-
AV004	2	0 (0.0)	-	-	-	-
AV005	2	0 (0.0)	-	-	-	-
AV006 Year One	131	18 (13.7)	H3N2	7	1	7
			B	12	-	11
AV006 Year Two	17	0 (0.0)	-	-	-	-
AV010	0	-	-	-	-	-
AV011	9	0 (0.0)	-	-	-	-
AV012 Year Two	1	0 (0.0)	-	-	-	-
AV015	55	3 (5.45)	H1N1	1	-	-
			B	1	-	-
			Influenza A	-	1[b]	-

[a]Vaccine Phenotype = cold adapted and temperature sensitive.
[b]Strain tested but not identifiable.
Table adapted from MedImmune, August 2002 CR response #48

Summary

Viral cultures obtained routinely from vaccinees, as well as from ill subjects yielded vaccine viruses. The contribution of the vaccine virus to the occurrence of illness early post-vaccination for these subjects is not easily assessed, in part because obtaining cultures from ill subjects in the early post-vaccination period (Day 0-10) has not been performed in a prospective, randomized, blinded fashion.

Shedding occurred commonly and transmission was observed, though it is difficult to quantify exactly based on the current data. When vaccine virus was recovered and examined, the cold

adapted and temperature sensitive phenotypic markers of the vaccine viruses were retained, even though nucleotide changes were identified in the vaccine viruses shed by recipients. In the limited number of isolates tested, reassorting of the vaccine virus with wild type strains was not identified in circumstances in which wild type strains (primarily A/H3N2 and B) were known to be circulating.

2.8. Annual Lot Release - Clinical Testing

Study AV024: A Prospective, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety of a Monovalent Vaccine of a New 6:2 Reassortant in Healthy Adults.

Rationale

The manufacturing of FluMist begins with the preparation of the Master Virus Seed (MVS). The MVS for each strain is a reassortant virus containing six genes of the cold-adapted (*ca*), temperature-sensitive (*ts*) attenuated Master Donor Virus (MDV) and two genes, the HA and NA genes, from a wild-type isolate and is called a 6:2 reassortant. Maximal attenuation of the MVS is achieved when all six internal genes from the MDV are present; however, individual genes confer significant attenuating properties. Therefore, it is theoretically possible that a mutation in any of the six internal genes could result in significant loss of the attenuation phenotype. It is also possible that combinations of new HA and NA genes with the MDV internal genes could reduce or eliminate the attenuation phenotype. Although attenuation can be tested in animals, the current animal models, primarily the ferret model, are imperfect for predicting events in humans.

After selection of a new strain for the upcoming influenza season, evaluating its safety profile in a clinical trial in adults will provide additional safety data prior to release of the trivalent vaccine. The clinical trial design will ensure that the vaccine virus has sufficient attenuation in humans, as demonstrated by incidence of fever $\geq 101^{o}F$. In previous trials with FluMist in adults, the rate of fever in vaccine and placebo recipients has been similar. For example, in AV009 conducted in 4,561 healthy adults ages 18-64 years, fever $\geq 101^{o}F$ in the seven day post-vaccination occurred in 0.57% and 0.6% of FluMist and placebo recipients respectively. Thus, similar rates of fever in FluMist and placebo recipients would be expected in a clinical trial to evaluate a new MVS, provided there is no significant loss of attenuation. CBER anticipates that performing such a clinical trial will be indicated for lot release of all new MVS, until extensive experience with CAIV-T has been established.

Design

The primary objective of the study was to assess the safety of a new reassortant strain in approximately 300 healthy adults (randomized 4:1 vaccine to placebo) prior to the release of trivalent CAIV (FluMist). Safety was demonstrated by similar rates of fever (oral temp $\geq 101^{o}F$) in vaccine and placebo recipients. The primary safety phase of the trial was the first eight days (Days 0-7), and subjects were followed for 28 days for SAEs. A six-month check of study participants is planned for long-term safety monitoring.

Vaccines

Each 0.5ml dose contained 10^{7} $TCID_{50}$ of the new influenza strain for 2002-2003, B/Hong Kong/330/2001, in normal allantoic fluid (NAF) with SPG stabilizer. The placebo was NAF.

Procedures

Briefly, study enrollment, obtaining informed consent, review of medical history, health assessment including temperature, and vaccination with 15 minute observation were performed on Day 0 (Visit 1). Beginning on the night of vaccination and for the fourteen days after, the

subjects recorded daily temperature, reactogenicity events (REs), other AEs and use of concomitant medications. Safety worksheets were completed by the subjects, and daily or every other day collection of information was performed by study personnel during the first 7 days post-vaccination and on Day 15. REs were predefined AEs that may occur post-vaccination and included: fever, cough, runny nose, sore throat, irritability, headache, chills, vomiting, muscle aches, decreased activity (lethargy).
SAEs were defined consistently with other FluMist trials (as described in AV019 CSR) and were monitored through Day 28 by telephone contact in the first 8 days post-vaccination and on Day 29. Additionally, subjects will be contacted by telephone at 6 months post-vaccination to check for development of any new, serious or chronic medical conditions.

Statistical Methods
The primary endpoint of this study was fever, defined as oral temperature $\geq$ 101°F within the first seven days post-vaccination. Comparison of the rate of fever between the two treatment groups was based on the upper limit of the two-sided 95% exact CIs for the rate difference (vaccine minus placebo) evaluated against the pre-specified criterion of 5 percentage points. The objective of the study was addressed by evaluating this single primary endpoint of fever $\geq$ 101°F against the pre-specified criterion of 5 percentage points.

All other reported RE and other AEs that occurred within seven days post-vaccination and all reported SAEs during the study period (Day 0-28) were summarized for descriptive purposes.

With ~300 evaluable subjects, this trial had at least 98% power to rule out a rate increase of 5 percentage points assuming a 1% or less rate of fever in the control group, and the true difference between the treatment groups was zero.

Results
A total of 330 subjects were enrolled into this protocol in August 2002, and a summary of the primary data was submitted to CBER on September 27, 2002. The mean age for the FluMist recipients was 37.1 years, and for placebo subjects was 41.2 years. Approximately 90% of both treatment groups were Caucasian or Hispanic, with the remaining 10% being African American.

All 330 subjects provided complete safety data for the initial phase (Days 0-7) of the trial. One FluMist recipient (0.4%) reported fever $\geq$ 101°F, and no placebo subjects reported an oral temperature > 101°F. The upper bound of the two-sided 95% CI on the rate difference for fever $\geq$ 101°F was 2.3%, which is less than the pre-specified equivalence criterion of within 5%.

Generally, similar proportions of participants experienced each of the REs for Days 0 to 7. The largest observed difference was 4.9 percentage points for runny nose [9.5% for FluMist vs. 4.5% for placebo subjects (95% CI: -3.4, 10.5)]. The next most commonly reported REs were sore throat (6.1% in both treatment groups) and headache (6.1% of FluMist and 9.1% of placebo subjects). There were no SAEs reported in the Days 0-7 period.

For the 15 day post-vaccination period (Days 0-14), more FluMist subjects than placebo recipients reported any RE (22.7% vs. 16.7%, respectively). Two of the 264 (0.8%) FluMist recipients reported fever $\geq$ 101°F, compared to none of the placebo recipients. Similar proportions of subjects (1.5%) in both treatment groups reported fever $\geq$ 100°F. Runny nose was reported more frequently for FluMist subjects compared to placebo subject [10.6% vs. 6.1%, 95% CI: -4.3, 10.7]. As observed in the Days 0-7 period, sore throat and headache were the next most commonly observed REs. There were no SAEs reported in the Day 0-14 monitoring period.

Safety monitoring for the study participants continued through Day 28, and a follow-up safety check at six months post-vaccination is planned. The data from these later monitoring periods will be submitted to CBER.

AV024 – MVS Release Study Conclusions
The study met the pre-specified primary endpoint; no increase in fever $\geq$ 101°F was observed in recipients of the new monovalent B (B/Hong Kong/330/2001) strain compared to NAF placebo recipients. Additionally, no increase in the other solicited REs was observed in the Days 0-7 or Days 0-14 monitoring periods for the new B strain recipients as compared to placebo recipients.

This study supports that the new MVS safety profile in adults was consistent with that observed with previous CAIV strains in clinical trials. The feasibility of performing similar trials annually, as needed for evaluating new MVS, in humans was also demonstrated.

3.0 EFFICACY SUMMARY

The four studies in support of efficacy of FluMist that were submitted in the original BLA were presented at the July 2001 VRBPAC meeting. The four studies include two pediatric trials, AV006 and AV011, and two adult trials, AV003 and AV009. All four of these trials demonstrated efficacy or effectiveness of FluMist compared to placebo (NAF). A summary of the efficacy and effectiveness data from these trials is provided.

3.1 Summary of the Efficacy Trials Performed in Children

3.1.1 AV006: A Phase 3, Randomized, Double-blind, Placebo-controlled, Trial to Assess the Safety, Immunogenicity and Efficacy of Influenza Virus Vaccine, Trivalent, Types A&B, Live, Cold-Adapted (CAIV-T) in Healthy Children.

Study AV006 was a prospective, randomized, double-blind, placebo-controlled, multi-center trial conducted in the U.S. over two years, the 1996-97 and 1997-98 influenza seasons. During Year 1, 1602 healthy children 15 to 71 months of age (not had their 6th birthday) were randomized 2:1 to receive FluMist (N= 1070) or placebo (N = 532). Most subjects (N = 1304) received two doses of study vaccine given 60 $\pm$14 days apart. A subset of subjects (N= 288) primarily enrolled at two study sites (Baylor and Harbor-UCLA) received a single dose of study vaccine. The study was designed as a 2-year study with a single cohort recruited in Year 1 (receiving either a 1 dose or 2-dose regimen), and remaining in the same study group to be re-vaccinated with 1 dose in Year 2. The study was not planned as a comparison of the 1 *vs.* 2 dose regimens.

Primary Objectives
In Year 1, the primary objective was to demonstrate that children receiving a 2-dose primary vaccine regimen of Flumist are protected from culture confirmed influenza illness caused by community-acquired subtypes antigenically similar to those contained in the vaccine for the influenza season directly following vaccination.

In Year 2, To demonstrate the efficacy of a 2nd year's single dose of Flumist to protect children who received a 1 or 2-dose primary vaccination regimen of Flumist in the previous year against community-acquired subtypes antigenically similar to those contained in the vaccine for the influenza season directly following the 2nd year's vaccination.

The **primary efficacy endpoint** was the first episode of culture-confirmed community-acquired influenza in a study participant following the 2nd dose of vaccine or placebo in Year 1.

Case Definition - A culture-confirmed case of influenza illness (criteria listed under Illness Surveillance) was one that occurred at least 15 days after receiving the 1st dose of vaccine or placebo and that was defined by a positive culture of a wild-type virus subtype antigenically similar to one contained in the vaccine.

In addition to the primary objective, the study evaluated several secondary objectives as assessments of the effectiveness and efficacy of FluMist, which are not discussed in this summary.

Vaccines
The1996-97 influenza strains contained in the vaccine were A/Texas/36/91 (H1N1), A/Wuhan/359/95 (H3N2) and B/Harbin/7/94-like. The 1997-98 strains were A/Shenzhen/227/95 (H1N1), A/Wuhan/359/95 (H3N2) and B/Harbin/7/94-like.

Illness Surveillance and Efficacy Assessments
Active surveillance was based upon regular phone contacts with the parents/guardians of the children. Initially calls were made every 2-3 weeks starting on the 11th day after the first vaccination. Once an influenza outbreak was declared at the site (as documented by influenza positive cultures from the study site laboratory or the local public health laboratory), the calls were increased to at least once every 7-10 days. The sponsor reports that from November 1996 through March 1997, the influenza outbreak periods, 95.9–96.9% of participants were successfully contacted at least once during each month.

For illness evaluations, parents were instructed to call the study site if their child had any illness consistent with influenza. The criteria for performing viral cultures, prior to influenza season, were 2 signs or symptoms in category "a" OR ≥ 1 sign or symptom from category "b", as follows:

a. Category
   - Fever (≥ 101°F rectal or oral; or 100.4 °F axillary),
   - Wheezing,
   - Shortness of breath,
   - Pneumonia,
   - Ear infection (acute otitis media), suspected or diagnosed.

b. Category
   - Runny nose or nasal congestion,
   - Sore throat (pharyngitis),
   - Cough,
   - Muscle aches,
   - Chills,
   - Headache,
   - Irritability,
   - Decreased activity,
   - Vomiting

Once influenza season began, criteria for viral culture were 1 sign or symptom in category "a" or 2 from category "b." A viral culture could also be performed at the discretion of the investigator. Viral cultures were performed locally, positive specimens were sent to Aviron (MedImmune) for official determination, including subtyping of all isolates and phenotyping for those isolated within 28 days of vaccination.

Statistical Methods
Efficacy point estimates were calculated in customary fashion:
100 x (1-relative risk of vaccinee becoming a case) =
100 x (1- P_v/ P_p); where P_v=proportion of vaccinees and P_p=proportion of placebo.

Confidence intervals (CI) were calculated using the method of Koopman for the ratio of binomial proportions.

AV006 – Results
Enrollment and Demographics
A total of 1602 subjects were enrolled; 85% were Caucasian and 52% were female. Generally, the FluMist and placebo groups were balanced for demographic characteristics.

Efficacy for Year 1
A total of 3127 cultures were obtained from all subjects. Of the 3127 cultures, 139 positive cultures for influenza were reported to the statistical center. One of the 139 cultures was lost in shipment and could not be confirmed by the sponsor's lab. In total, 114 positive cultures obtained from 108 subjects were positive for types A/H3N2 or B. Of the 114 positive cultures, 14 were in Flumist recipients (n=11 in the 2-dose and n=3 in the1-dose regimen) and 100 were in placebo recipients (n=86 for 2-dose and n= 14 in the 1-dose regimen). The efficacy estimates for all study participants by dosing regimen are shown in Table 3.1a.

Six placebo recipients had positive cultures for type A/H3N2 and later had positive cultures for type B. These subjects contributed a single event to "any strain" analysis and a single event to both H3N2 and B analyses. There were 18 positive cultures obtained within 14 days of Dose 1 and thus, not included in the primary efficacy analysis by definition. All 18 isolates phenotyped as CAIV strains. Five subjects had two positive cultures (obtained 3-5 days later) for the same virus, and only the 1st isolate was counted in the analysis.

Table 3.1a. AV006 - Year 1 Efficacy of FluMist in Preventing Culture-Confirmed Influenza Illness for All subjects (15 through 71 months of age) by Dosing Regimen.

Analysis Group	Strain	Estimated Efficacy % (95% CI)
Participants Receiving Two Doses	Any	93.4 (87.5, 96.5)
	H3N2	96.0 (89.4, 98.5)
	B	90.5 (78.0, 95.9)
Participants in Two Dose Regimen	Any	93.2 (87.6, 96.3)
	H3N2	95.5 (89.3, 98.1)
	B	90.5 (78.0, 95.9)
Participants in One Dose Regimen	Any	88.8 (64.5, 96.5)
	H3N2	86.9 (46.6, 96.8)
	B	91.3 (45.6, 98.6)
All Randomized Participants	Any	92.6 (87.3, 95.7)
	H3N2	94.5 (88.3, 97.4)
	B	79.5 (79.5, 95.7)

Table from MedImmune, original BLA, October 2000, Volume 16.

Wild type A/H1N1 did not circulate in the community and no field efficacy data were generated for this strain.

The number of cases and efficacy estimates for subjects in age subgroups for Year 1 are shown on Table 3.1b. In these analyses, FluMist had demonstrable efficacy against "any strain" influenza (included A/H3N2 and B strains) for children in each of the age groups, including

those from 60 through 71 months of age. The data for subjects from 60 through 71 months (N=312) are the only efficacy data for children in the 5 - 17 year age group.

Table 3.1b. AV006 – Year 1: Efficacy Estimates and the Number of Cases (n) and Totals (N) Included in the Efficacy Evaluations of FluMist by Age, Gender, and Race/Ethnicity.

Category	FluMist n/N	Placebo n/N	Total n/N	Any Influenza % Efficacy (95% CI)
Age (mos.)				
<24	4/173	15/99	19/272	84.7 (57.5, 94.6)
24–35	2/225	31/134	33/359	96.2 (85.8, 99.0)
36–47	5/231	16/96	21/327	87.0 (66.8, 94.9)
48–59	0/224	18/108	18/332	100 (89.9, 100)
?**60 to 72 mos**	3/217	14/95	17/312	90.6 (70.3, 97.1)
Gender				
Female	9/571	52/272	61/843	91.8 (83.8, 95.8)
Male	3/499	42/260	45/759	93.8 (85.0, 97.4)
Race/Ethnicity				
White	13/906	84/449	97/1355	92.3 (86.5, 95.7)
Non-White	1/164	10/83	11/247	94.9 (70.0, 99.2)

Table from MedImmune, August 2002 response #49

Efficacy for Year 2

The procedures for monitoring efficacy and case definitions in Year 2 were the same as used in Year 1.

The characteristics of the two treatment groups at the time of enrollment into Year 2 were similar: the mean age was 55 months and 52 months; 86% and 85% were Caucasian; and 54% and 51% were female, FluMist and placebo groups respectively. As compared to subjects who chose not to participate, Year 2 participants were more likely to have a primary caretaker working outside of the home (51% *vs* 39%). Otherwise, the participants in Year 2 were comparable to non-participants.

During Year 2 influenza season, 1808 cultures were obtained, 1188 in the FluMist group and 620 in the placebo group. Of the 1808, 71 (4%) cultures were positive for influenza, 15 (1%) of the FluMist recipient cultures and 56 (9%) of placebo recipient cultures. The efficacy following FluMist for all study participants by dosing regimen is shown in Table 3.1c.

In the primary efficacy analysis, the efficacy estimate was 100% (95% CI: 63, 100) against wild-type strains "antigenically similar" to vaccine strains. The predominant circulating strain in Year 2 was A/Sydney (H3N2); however, these isolates were not included in the primary analysis since this type A was considered to be an antigenic variant. In Year 1 the circulating A/H3N2 strain was more closely matched to the A/Wuhan (H3N2) vaccine strain. While the protocol did not pre-specify the definition of antigenic similarity, in the CR responses the sponsor indicated that CDC criteria based on $\leq$ four-fold fold difference in HAI titers in a ferret model was used.

H1N1 did not circulate in the community in Year 1 or Year 2, and no field efficacy data were generated for this strain.

Table 3.1c AV006 – Year 2: Efficacy of FluMist in Preventing Culture-Confirmed Influenza Illness for All subjects (15 through 71 months of age) by Dosing Regimen.

Analysis Group	Strain	No. of Isolates		Estimated Efficacy
		FluMist	Placebo	% (95% CI)
All Year Two Participants	All community acquired strains	15	56	87.1 (77.7, 92.6)
	Strains in FluMist [A/Wuhan (H3N2), B]*	0	5	100 (63.1, 100)
	A/Sydney (H3N2)	15	51	85.9 (78.0, 91.9)
Participants Enrolled in the Two-Dose Regimen in Year One	All community acquired strains	14	52	87 (77.0, 92.6)
	Strains in FluMist [A/Wuhan (H3N2), B]	0	4	100 (53.7, 100)
	A/Sydney (H3N2)	14	48	85.9 (75.0, 92.1)
Participants in One-Dose Regimen in Year One	All community acquired strains	0	4	100 (54.9, 100)
	Strains in FluMist [A/Wuhan (H3N2), B]	0	4	100 (54.9, 100)
	A/Sydney (H3N2)	0	3	100 (39.8, 100)

Table from MedImmune, original BLA submission, October 2000, Volume 16.

The number of cases and efficacy estimates for subjects by age groups for Year 2 are shown on Table 3.1d. In these analyses, FluMist had demonstrable efficacy against "any strain" influenza (included A/H3N2 and B strains) for subjects in each of the age subgroups, including 60 through 71 months of age. The data for subjects from 60 through 71 months (N=312) are the only efficacy data for children in the 5 - 17 year age group.

Table 3.1d Study AV006 Year Two: Number of Cases (n) and Totals (N) Included in the Efficacy of FluMist by Age, Gender, and Race/Ethnicity

Category	FluMist n/N	Placebo n/N	Total n/N	Any Influenza % Efficacy (95% CI)
Age (mos.)				
<24	0/0	0/0	0/0	NA
24–35	2/159	7/87	9/246	84.4 (35.2, 96.3)
36–47	4/186	15/108	19/294	84.5 (56.8, 94.5)
48–59	2/197	10/77	12/274	92.2 (69.0, 98.0)
?**60 to 72**	7/375	24/169	31/544	86.9 (70.8, 94.1)
Gender				
Female	12/492	30/225	42/717	81.7 (65.3, 90.4)
Male	3/425	26/216	29/641	94.1 (82.0, 98.1)
Race/Ethnicity				
White	14/787	54/377	68/1164	87.6 (78.1, 93.0)
Non-White	1/130	2/64	3/194	75.4 (-85.6, 96.7)

Table from MedImmune, August 2002 CR response #49

A. AV006 - Overall Efficacy Years 1 and 2 Combined

The overall efficacy for Years 1 and 2 combined are shown in Table 3.1e. Against all community-acquired strains, including A/Sydney (H3N2), which was an antigenic variant, the efficacy estimate was 91.1 (95% CI: 87.7, 94.4).

Table 3.1e Study AV006 – Overall Efficacy of FluMist In Year One and Two Combined for All Participants (15 through 71 months of age) by Dosing Regimen

Strain	No. Children with ? 1 Positive Culture		% Efficacy (95% CI)[c]
	FluMist[a]	Placebo[b]	
All community acquired strains (Wuhan, Sydney B)	29	147	91.1 (87.7, 94.4)
All H3N2	22	117	91.9 (87.2, 94.9)
All B	7	38	91.1 (80.1, 96.0)

[a] 1070 vaccinees in Year 1 and 917 returning in Year 2
[b] 532 placebo recipients in Year 1 and 441 returning in Year 2
[c] Based on Cox proportional hazards model account for drop-outs from Study AV006- Year 1 to Year 2.
Table adapted from MedImmune, January 2002 CR response

Efficacy against all community-acquired influenza strains (A/H3N2 and B) by age group for Years 1 and 2 combined are shown in Table 3.1f. For the subjects 60 months through 71 months of age, efficacy with 95% CI was 91.0% (77.9, 96.3).

Table 3.1f Efficacy of FluMist by Age Group* for AV006 Year One and Year Two Combined

Age (mos.)	Study Year	FluMist n/N	Placebo n/N	Total n/N	Any Influenza % Efficacy (95% CI)
<24	Year 1	4/173	15/99	19/272	
	Year 2	0/0	0/0	0/0	
	Combined	4/173	15/99	19/272	86.5 (63.7, 94.9)
24–35	Year 1	2/225	31/134	33/359	
	Year 2	2/159	7/87	9/246	
	Combined	4/384	39/221	42/605	93.6 (85.1, 97.3)
36–47	Year 1	5/231	16/96	21/327	
	Year 2	4/186	15/108	19/294	
	Combined	9/417	31/204	40/621	89.3 (76.4, 95.2)
48–59	Year 1	0/224	18/108	18/332	
	Year 2	2/197	10/77	12/274	
	Combined	2/421	28/185	30/606	94.7 (85.1, 98.1)
? **60-71**	Year 1	3/217	14/95	17/312	
	Year 2	7/375	24/169	31/544	
	Combined	10/592	38/264	48/856	91.0 (77.9, 96.3)

*The number of participants in each age group derived from Table 3.1b for Year 1 and Table 3.1d for Year 2.
Table adapted from MedImmune, November 2002 correspondence

Summary of AV006

Efficacy following FluMist was demonstrated against culture-proven influenza illness due to circulating strains of influenza, A/H3N2 and B in Years 1, 2 and both years combined in AV006. Among the1602 healthy children age 15 months through 71 months enrolled, 544 subjects were 60 through 71 months of age. Although the number of subjects evaluated in the 60 through 71 month age group was small, efficacy was demonstrated against the circulating strains of influenza.

No data from clinical trials to assess the efficacy or effectiveness following FluMist in children age 6 years through 17 years have been submitted to the BLA.

3.1.2 Study AV011: A Phase 3, Randomized, Prospective, Open-label Challenge Study to Assess Viral Shedding of Influenza Virus Vaccine, Monovalent, Type A, Live, Cold-Adapted (CAIV-M) in Healthy Children.

Design
In Study AV006, no A/H1N1 wild-type influenza virus circulated during Year 1 or Year 2 of the trial. Thus, no field efficacy data were generated for FluMist against influenza illness due to A/H1N1strains. Study AV011 was designed as an open-label "challenge" study, with protection against shedding of CAIV-M used as a surrogate of vaccine efficacy. A subset of AV006 participants (FluMist and placebo recipients) received one intranasal dose of cold-adapted monovalent A/H1N1 vaccine strain (CAIV-M). The study was performed in the late Spring of 1998, approximately 5 - 8 months after receipt of study vaccine in Year 2, and no wild-type influenza was circulating in the communities. The proportion of subjects (prior FluMIst vs. prior placebo recipients) with shedding of the CAIV-M strain was compared. A total of 1342 subjects were eligible for AV011, from the same 10 sites that participated in AV006.

Primary Efficacy Endpoint
The primary efficacy endpoint was the percent of subjects with shedding of CAIV-M on Days 1, 2, 3 or 4.

Viral shedding for the primary analysis was defined as at least one positive culture from Days 1, 2, 3, or 4 post-vaccination. Vaccine efficacy against viral shedding was calculated as:
[1- (event rate in prior vaccinees/event rate in prior placebo recipients)] x 100%.

Confidence limits were computed using Koopman's method for the confidence intervals on the ratio of two binomial proportions.

Other Endpoints
Additional secondary endpoints for efficacy were identified, but are not discussed in this summary.

Vaccine
The A/H1N1 CAIV-M vaccine strain was Type A/Shenzhen/227/95 (H1N1) with each 0.5 ml dose contained 10^7 $TCID_{50}$ of vaccine virus in NAF. This was the same A/H1N1 vaccine strain incorporated in the AV006 - Year 2 FluMist formulation.

Virologic Monitoring
Subjects had nasal and throat swabs obtained for culture on post-vaccination days 1, 2, 3 and 4 to assess shedding of CAIV-M vaccine strain. Both swabs were placed into the same tube of transport medium and the inoculated media were divided into three aliquots. If the study site isolated influenza, one of the frozen aliquots was sent for quantitative assay with results reported in plaque-forming units per milliliter (pfu/ml) of A/Shenzhen/227/95.

AV011 Results
Enrollment and Demographics
A total of 222 subjects (~ 20 subjects from each site) were enrolled; prior FluMist recipients, N=144; prior placebo recipients N=78. Of the 144 FluMist recipients, 128 had received the 2-dose regimen and 16 received the 1-dose regimen in Year 1 of study AV006. Of the 78 prior placebo recipients, 71 had received the 2-dose regimen and 7 the 1-dose regimen in Year 1. AV011 participants were similar to AV011 non-participants as noted by comparison of the demographics at the time of enrollment into AV006 (data not shown).

Viral Shedding

Nasal and throat swabs were obtained from 97-100% of each group (prior FluMist and prior placebo subjects) on Days 1, 2, 3 and 4 post-vaccination. The number of subjects with shedding on each day, and the efficacy estimates based upon viral shedding are shown in Table 3.1.2a. Efficacy (95% CI) was 82.9% (60.2%, 92.7%) for all subjects, combining FluMist subjects in the one-dose and two-dose regimens. Among prior Flumist recipients, 4% had shedding at any time as compared to 25% shedding in prior placebo recipients. Rates of viral shedding the 10 study sites varied from 0% to 25%.

Table 3.1.2a AV011 – Efficacy as Determined by A/H1N1 Shedding After Challenge with CAIV-M (A/H1N1) by Treatment Group

	Prior FluMist (N= 144)	Prior Placebo (N=78)	Efficacy % (95% CI)
Shedding on Any Day, N (%)	6 (4)	19 (25)	82.9 (60.2, 92.7)
Shedding on Day, N (%)			
1	2 (1)	2 (3)	
2	5 (3)	10 (13)*	
3	1 (0.7)	9 (12)*	
4	0 (0)	6 (8)*	

* Statistically significant ($p<0.05$)
Table combines Year 1 one-dose and two-dose recipients.
Table adapted from MedImmune, original BLA submission October 2000, Volume 41.

On Day 4, 6 placebo recipients had viral shedding, but no cultures were taken after Day 4, so total duration of shedding cannot be determined. With this limitation, the mean duration of shedding in the first 4 days post-vaccination was significantly reduced in the prior FluMist group compared to the prior placebo group (respectively 0.06 ± 0.3 vs. 0.3 ± 0.7, $p=0.0001$).

AV011 - Summary

No field efficacy data were generated for A/H1N1 strain, as it was not circulating during the two years of the pediatric efficacy trial, AV006. Study AV011 evaluated the shedding of CAIV-M vaccine strain following challenge, as a surrogate of efficacy. The sponsor reviewed the literature of pediatric challenge studies and field trials, which have shown that reduction in shedding of challenge CAIV may be a useful surrogate for vaccine efficacy. The reference that most directly addresses the utility of this challenge model is from the multi-year influenza vaccination study at Vanderbilt University (Neuzil et al, Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985-1990: the pediatric experience. 2001 *Pediatr Infect Dis J,* 20: 733-740). In the Vanderbilt trial, three different CAIV vaccine strains were used for vaccination of children and subsequent challenge: A/Kawasaki/9/86 (H1N1), A/Bethesda/1/85 (H3N2) and A/Washington/897/80 (H3N2). In each case, vaccination protected against subsequent challenge with the corresponding monovalent CAIV strain. The sponsor states that each CAIV strain proved protective against natural infection, and they view these experiences as supportive of the utility of the challenge model as a surrogate of efficacy. Although these historical experiences are of interest, CBER does not view the challenge model using a vaccine strain as having been validated for use as a surrogate of efficacy.

No data to assess directly the field efficacy against A/H1N1 for the strains contained in current FluMist formulations have been submitted to the BLA.

3.2 Summary of the Efficacy Trials Performed in Adults

3.2.1 STUDY – AV009 A Prospective, Randomized, Double-blind, Placebo-controlled, Trial to Assess the Safety, Tolerability, and Effectiveness of Influenza Virus Vaccine, Trivalent, Types A and B, Live, Cold-Adapted (CAIV-T) in Healthy working Adults to Reduce Influenza-Like Illness, Absenteeism from Work and Health Care Costs During Influenza Outbreaks.

Design

This trial was performed to assess the safety, tolerability, and effectiveness of FluMist to support an indication for use of the vaccine in healthy working adults, ages 18 through 64 years. Subjects had to work outside of the home ≥ 30 hours/week for a single employer, have health insurance and availability by telephone.

This was a prospective, randomized, double-blind, placebo-controlled, multi-center trial conducted at 13 study sites in the U.S. during the 1997-1998 influenza season. Subjects were randomized 2:1 to receive FluMist or placebo.

Primary Effectiveness Objective

- To show a smaller proportion of the FluMist participants has any febrile illness (AFI) during influenza outbreaks than the placebo recipients.

Secondary Effectiveness Objectives

- During influenza outbreaks, healthy working adult CAIV-T recipients compared to placebo recipients had lower average:
  - Number of days of illness-associated absenteeism from work,
  - Number of days of illness-associated medically attended illnesses,
  - Number of illness episodes, and
  - Number of days of illness episodes

Monitoring

Effectiveness (Clinical Efficacy)

Subjects were provided with monthly effectiveness diary cards (months November – March) to record illness information. Automated telephone calls were made approximately every 2 weeks to remind subjects to complete and return these cards.

The monthly diary card had 3 sections to capture effectiveness measures:
Sections 1A - queried for fever, runny nose, sore throat, cough, h/a, muscle aches, chills, and tired/weak.
Section 1B - queried for healthcare utilization or missed work because of symptoms in Part 1A as follows: "I took an over-the-counter (OTC) medication," "I went to a healthcare provider (HCP)," "I had a medical test done," "I took a prescription antibiotic," "I took a non-antibiotic prescription medication," "I was hospitalized," "I was less effective at my job," and " I missed work."
Section 2 - queried for healthcare utilization for illness other than those in Part 1A, as follows: "I went to a HCP," "I had a medical test done," "I took a prescription antibiotic," " I took a non-antibiotic prescription," "I was hospitalized," and "I missed work."

Study Endpoints

Primary effectiveness endpoint

Occurrence of any AFI. Participants were counted as reaching this endpoint if:

- They had at ? 2 consecutive days of symptoms in Part 1A of the diary
- One of the symptoms on at least one of the days was fever, and
- There must have been at least 2 symptoms present on one day.

Secondary effectiveness endpoints

The secondary effectiveness objectives were to assess the effect of FluMist on complications associated with AFIs as measured by absenteeism from work and medically attended illness.

- Number of days of AFI-assoc. absenteeism. The number of missed workdays checked in Part 1B of the diary that overlapped with AFI episodes.
- Number of days of AFI-associated medically attended illness (MAI). The number of days for which at least 1 MAI (went to a health-care provided, had a medical test done, took a prescription medication or antibiotic, or was hospitalized) occurred during an AFI was calculated.
- Number of AFI episodes. The number of AFI episodes that occurred during an outbreak for each participant.
- Days of AFI episodes. For each participant, the total number of days was counted by summing the duration of each episode, and duration was calculates as follows: start date - stop date +1.

Other Illness Definitions

- Upper Respiratory Infection (URI). The participant must have had two consecutive days of URI symptoms in part 1A of effectiveness diary card.
- Febrile URI (FURI): as above and in addition, fever must have been present on at least one day.
- Severe Febrile Illness (SFI): If there were at least 3 days of symptoms for part 1A of effectiveness diary card, fever on at least one day, and at least 2 symptoms on all three days.

In addition to these pre-specified definitions, three other definitions were applied to data in post-hoc analyses:

- CDC influenza-like illness (ILI) – fever plus either cough or sore throat, must be present on the same day or on consecutive days.
- Dept of Defense (DoD ILI) – cough plus either fever or chills, also must be present on the same day or consecutive days.
- Aviron ILI (AV ILI) – 1) 2 consecutive days of symptoms, 2) at least 1 day of fever, 3) > 1 URI symptom, 4) at least 1 non-febrile systemic symptoms and 5) > 2 symptoms on at least 1 days.

Influenza outbreaks were identified in the community using a pre-defined algorithm. All of the illness-associated endpoints were analyzed during influenza outbreaks, for the entire study period (11/1/97 – 3/31/98), and in post-hoc analyses to site-specific influenza outbreak periods, and to a pooled, 14-week outbreak period 12/14/97-3/21/98. Additionally, all of these endpoints were applied to febrile upper respiratory tract infections (FURIs), severe febrile illness (SFI) and all URIs during influenza outbreaks, as well as during the entire study period.

Additional secondary effectiveness objectives were evaluated, but are not discussed in this summary.

AV009 Results – Effectiveness Endpoints

Enrollment and Demographics

A total of 4561 (FluMist n= 3041 and placebo n=1520) subjects were enrolled. The demographic characteristics of the two treatment groups were similar; each group was composed of 54% females, ~84% Caucasians and ~ 47% had a Bachelor's Degree or higher.

Effectiveness

No significant difference in effectiveness was observed between the FluMist and placebo groups in the primary analysis of effectiveness, i.e., occurrence of any febrile illness (AFI) during Site-Specific Outbreak Periods. Severe Febrile Illness (SFI) and febrile URIs (FURI) were less common in the FluMist than placebo group. Post-hoc analyses applied to the data revealed significantly fewer CDC-ILI and DoD-ILI in the FluMist recipients (Table 3.2.2d).

Table 3.2.2d Percentage of Participants Having One or More Illness Events During the Site-Specific Outbreak Periods

Occurrence of	FluMist N=2,833	Placebo N=1,420	Percent Reduction	95% CI[a,b]
Any Febrile Illness[c]	13.2	14.6	9.7	(-5.8, 22.8)
Severe Febrile Illness	10.1	12.2	17.4	(1.3, 30.8)
Febrile Upper Respiratory Illness	8.5	10.8	21.9	(5.3, 35.5)
CDC-Defined Influenza-like Illness[d]	10.7	13.9	23.2	(9.1, 35.0)
DoD-Defined Influenza-like Illness[d]	10.4	13.7	23.5	(9.4, 35.4)

[a]Asymptotic two-sided 95%-confidence interval on percent reduction using Koopman's method.
[b]Unadjusted for multiple comparisons.
[c]The primary endpoint of the study.
[d]Post hoc analysis
Table adapted from MedImmune, January 2002 CR response #109.

The rate of AFI episodes (number of AFI episodes/1000 subject per 7-week outbreak period) was not significantly different between the FluMist and placebo groups: 151.3 FluMist *vs.* 168.1 placebo. However, the rates of SFI and FURI were significantly different (Table 3.2.2e).

Table 3.2.2e Rate of Illness Episodes during the Site-Specific Outbreak Periods

Episodes of[a]	FluMist N=2,833	Placebo N=1,420	Percent Reduction	95% CI[b,c]
Any Febrile Illness	151.3	168.1	10.0	(-2.1, 20.7)
Severe Febrile Illness	111.0	136.7	18.8	(7.4, 28.8)
Febrile Upper Respiratory Illness	92.4	121.0	23.6	(12.7, 33.2)
CDC-Defined Influenza-like Illness[d]	119.2	156.1	23.6	(13.2, 32.8)
DoD-Defined Influenza-like Illness[d]	116.6	155.4	24.9	(14.7, 33.9)

[a]Number of episodes of illness per 1,000 participants per 7-week outbreak period.
[b]Based on Poisson regression.
[c]Unadjusted for multiple comparisons.
[d]Post hoc analysis
Table adapted from MedImmune, January 2002 CR response, #109.

The rates of AFI-associated events for all study participants are shown on Table 3.2.2f. Significant decreases were observed in days of HCP visit, taking a prescription antibiotic and for taking any prescription medication for FluMist recipients compared to placebo subjects.

Table 3.2.2f 1Rate of AFI-Associated Events during the Site-Specific Outbreak Periods

Endpoint[a]	FluMist N=2,833	Placebo N=1,420	Percent Reduction	95% CI[b,c]
Days of OTC Medication Use	576.9	752.3	23.3	(12.0, 33.2)
Days With At Least One Health-care Provider Visit	44.0	51.5	14.7	(-0.3, 27.5)
Days Taking At Least One Prescription Antibiotic	195.6	342.9	42.9	(33.1, 51.3)
Days Taking Any Prescription Medication	250.0	413.9	39.6	(29.5, 48.2)

[a]Rates are given in units of number of days (or number of events as appropriate) per 1,000 participants per 7-week outbreak.
[b]Based on Poisson regression
[c]Unadjusted for multiple comparisons.
Table adapted from MedImmune, January 2002 CR response #109.

Analyses for Age Subgroups

The number of subjects enrolled by age group (in decades) is shown in Table 3.2.2g. The highest percentage of subjects enrolled were in the 30-39 year decade, followed by the 40-49 year group with these two groups providing 61.3% of subjects. The sample size in the 50-59 year age group is small (N=380 FluMist recipients). Of note, few subjects in the 60-64 year age group (FluMist N= 49) were enrolled.

Table 3.2.2g Number of Subjects Enrolled in Study AV009 by Age Group In 10-Year Intervals by Treatment Group

Age Category	FluMist N=3041 n (%)	Placebo N=1520 n (%)	All N=4561 n (%)
18–29 years	747 (16.4)	375 (8.2)	1122 (24.6)
30–39 years	998 (21.9)	486 (10.7)	1484 (32.5)
40–49 years	857 (18.8)	457 (10.0)	1314 (28.8)
50–59 years	390 (8.6)	181 (4.0)	571 (12.5)
60–69 years[a]	49 (1.1)	21 (0.5)	70 (1.5)

[a]No participants enrolled were >65 years of age.
Table from MedImmune January 2002 CR response #112

In a post-hoc analysis for the subset of 641 adults 50 years of age or older (439 FluMist and 202 placebo recipients), the occurrence of illness and the days of illness were not significantly reduced for AFI, SFI, FURI or CDC-ILI. In some of these analyses, negative effectiveness was observed. In the secondary analyses, illness-associated days of missed work, healthcare provider visits, and antibiotic use were significantly reduced for the three pre-specified febrile illness definitions of AFI, SFI, and FURI, as well as for CDC-ILI (Table 3.2.2h). No reduction in OTC medication use was observed.

Comparison of the outcomes for subjects < 50 years of age and those $\geq$ 50 years are shown in Table 3.2.2h. There were significantly greater reductions for those ? 50 years compared to those < 50 years of age for illness associated days of missed work for AFI (p=0.01) and SFI (p=0.03) and for illness associated days of healthcare provider visits for all three febrile illness

definitions. These findings should be evaluated acknowledging that no significant reductions in the occurrence of the three illness categories were observed for the subjects ≥ 50 years of age.

Summary of AV009

Although statistically significant effectiveness was not observed against the illness category of "any febrile illness," FluMist demonstrated effectiveness against more specific illness definitions of SFI and FURI, as well as for CDC-ILI in post-hoc analysis, for the entire study cohort ages 18 through 64 years. For the analyses by age subgroups, no significant decrease in the occurrence of any of these illnesses for the subjects ≥ 50 years of age was observed, and negative effectiveness estimates were observed for some outcomes. For the illness-associated outcomes (missed work days, HCP visits, and antibiotic use) a significant reduction was noted for all study participants, and in some analyses the reduction was significantly greater for the subjects ≥ 50 years of age compared to those < 50 years, even though no decrease in the occurrence of the illnesses was observed in the older subjects. Few subjects over 50 years age were enrolled, which limits interpretation of the statistical comparisons.

Table 3.2.2h Percent Reduction (and 95% Confidence Intervals) in Illness Categories and Illnesses-Associated Outcomes in Subjects < 50 years and Subjects 50 – 64 Years of Age in Study AV009

	Any Febrile Illness		Severe Febrile Illness		Febrile URI		CDC ILI	
	<50 Years N=3920	?50 Years N=641	<50 Years N=3920	?50 Years N=641	<50 Years N=3920	?50 Years N=641	<50 Years N=3920	?50 Years N=641
Illness								
Occurrence of:	10.9 (-5.1, 24.4)	-7.3 (-81.2, 35.8)	19.5* (3.0, 33.2)	-7.3 (-91.1, 39.2)	23.7* (6.7, 37.5)	-3.4 (-98.4, 45.5)	24.4* (9.8, 36.6)	8.1 (-57.4, 45.8)
Episodes of:	11.2 (-1.5, 22.4)	-7.0 (-55.7, 26.4)	20.4* (8.5, 30.9)	-1.1 (-48.2, 31.0)	25.9* (14.5, 35.8)	-7.8 (-61.7, 28.1)	25.2* (14.2, 34.7)	5.0 (-37.8, 34.5)
Days of:	22.9* (11.3, 33.0)	19.8 (-16.3, 44.7)	27.7* (16.7, 37.5)	21.5 (-14.6, 46.2)	25.2* (13.1, 35.7)	18.0 (-22.1, 44.9)	29.9* (19.1, 39.3)	25.4 (-8.5, 48.8)
Illness associated days of:								
Missed work	6.1 (-10.6, 20.2)	45.7* (20.6, 62.9)	12.0 (-3.9, 25.4)	46.1* (20.2, 63.5)	26.6* (13.1, 38.0)	38.4* (6.9, 59.2)	12.9 (-2.9, 26.3)	49.6* (25.9, 65.7)
Reduced work effectiveness	17.0* (3.5, 28.7)	44.0* (18.4, 61.5)	22.1* (9.1, 33.3)	45.3* (19.6, 62.7)	23.4* (10.0, 34.7)	32.0 (-2.2, 54.8)	18.7* (4.9, 30.5)	45.6* (20.2, 62.8)
HCP visits	4.9 (-13.5, 20.2)	74.3* (59.9, 83.6)	17.8* (2.0, 31.0)	71.1* (54.9, 81.5)	36.9* (24.4, 47.3)	69.2* (51.6, 80.4)	11.1 (-6.4, 25.7)	71.1* (55.2, 81.4)
Antibiotic Rx	40.9* (29.9, 50.2)	59.6* (38.0, 73.6)	45.7* (35.4, 54.3)	57.4* (34.5, 72.3)	45.1* (34.2, 54.1)	41.7* (8.9, 62.7)	34.7* (22.2, 45.2)	56.3* (32.9, 71.5)
Any Rx	36.8* (25.3, 46.5)	58.0* (36.7, 72.1)	41.6* (30.9, 50.7)	56.7* (34.6, 71.3)	39.2* (27.5, 49.0)	46.9* (19.0, 65.2)	31.9* (19.2, 42.6)	56.0* (33.7, 70.8)
OTC	25.3* (13.5, 35.5)	-2.3 (-55.6, 32.8)	29.8* (18.4, 39.6)	1.8 (-49.7, 35.6)	29.7* (18.0, 39.8)	8.8 (-40.5, 40.8)	30.6* (19.5, 40.2)	-1.4 (-55.0, 33.6)

Table adapted from MedImmune, January 2002 CR response #110 and 111 and November 2002 correspondence.
*p <0.05

3.2.2 STUDY AV003: A Phase 3 Double-blind, Placebo-Controlled Challenge Study to Assess the Efficacy of Cold-Adapted Influenza Virus Vaccine, Live Trivalent (CAIV-T, FluMist) in Healthy Adults

AV003 was conducted to assess the efficacy of FluMist and of the trivalent inactivated influenza vaccine (TIV) in protecting subjects from laboratory diagnosed influenza disease following a challenge with a wild-type influenza virus. This study was performed early in the clinical development of FluMist. Originally the study was performed to establish that FluMist was protective in seronegative adults and thus, merited evaluation in field trials in the pediatric population. The study was also submitted to provide evidence of efficacy against A/H1N1 influenza strain as no H1N1 virus circulated during the field efficacy studies, AV006 and AV009.

DESIGN

AV003 was a randomized, double-blind, placebo-controlled challenge study performed in healthy adults, 18-41 years old from 12/11/95 through 2/15/96. Subjects were immunized with FluMist, TIV or placebo and then 28 days later received intranasal challenge with wild-type influenza (the strain to which the subject was serosusceptible) to assess protection. Serosusceptible was defined as a strain-specific HAI titer $\leq$ 1:8.

OBJECTIVES

- To assess the efficacy of FluMist compared to placebo post-challenge with wild type influenza against laboratory-documented influenza illness.
- To assess the efficacy of FluMist compared to trivalent inactivated influenza (TIV - Fluvirin® manufactured by Evans Medeva) post-challenge with wild type influenza against laboratory-documented influenza illness.
- To assess the safety and immunogenicity of FluMist in adults serosusceptible to at least one of the virus strains (H1N1, H3N2, and B) contained in the influenza vaccines (FluMist and TIV).
- *Post-hoc:* To assess the reduction of viral shedding post-challenge with wild type influenza.

Laboratory-documented illness was defined: symptoms of influenza accompanied by wild-type viral shedding on one or more days and/or $\geq$ 4-fold rise in HAI antibody to the challenge virus from Day 28 to Day 56.

Illness was defined: $\geq$ 1 respiratory symptom of moderate or greater severity OR $\geq$ 2 respiratory symptoms of any severity on 2 consecutive days. Respiratory symptoms include nasal stuffiness, runny nose, earache, sore throat, hoarseness, or difficulty breathing (not due to stuffiness). Subjects with myalgias or fever were defined as having "influenza-like illness."

Primary Efficacy Endpoint

The primary measure of protective efficacy of FluMist was the difference between the rates of laboratory-documented influenza illness in the FluMist and placebo groups. FluMist would be considered protective if, after wild-type challenge, the rate of laboratory-documented illness in the FluMist group was significantly less than the rate in the placebo group (2 sided p-value $\leq$ 0.05). With the enrolled sample size (~ 30 per group), the study had about 90% power to detect a difference in rates of laboratory-documented influenza if the true rate for the placebo group and FluMist group were 50% and 10% respectively.

VACCINES AND CHALLENGE STRAINS

1. FluMist –The 1994-95 strains were H1N1 A/Texas/36/91-like; H3N2 A/Shandong/9/93; Type B Panama/45/90. Each 0.5 ml dose contained 10^7 $TCID_{50}$ of each strain of virus in NAF.
2. Trivalent inactivated influenza vaccine (TIV) – The licensed vaccine (0.5ml dose) from Evans Medeva also contained the recommended 1994-95 strains.
3. Challenge viral strains – Each 0.5 ml (0.25 ml per nostril) challenge dose contained 10^7 $TCID_{50}$ of one of the following strains: H1N1 A/Texas/36/91 – Wild type; H3N2 A/Shangdong/9/93-Wild type or B/Panama/45/90-Wild type. The challenge strains were delivered by nasal drops.
4. Placebos
   a. Intranasal - NAF in SPG, lot CAE008 was used.
   b. Injectable – saline (PBS with 0.1% thimerosal)

Table 3.2.2a AV003 - Vaccine Study Groups

		Study Vaccines	
Treatment Group	**Number Enrolled**	**Intranasal Spray**	**IM Injection**
FluMist	36	FluMist	Saline
TIV	33	NAF	TIV
Placebo	34	NAF	Saline

Table generated by CBER

Approximately four weeks after vaccination, subjects had nasal wash samples and serum samples obtained for antibodies to influenza. Then, the subjects who participated in the challenge phase received an intranasal challenge with the homologous strain to which they had been serosusceptible at screening (challenge strains listed above). The participants were then sequestered for seven days. During sequestration, subjects received limited physical exams, had their temperatures measured twice a day, and underwent daily nasal washes for viral isolation.

RESULTS

Enrollment and Demographics

A total of 383 subjects were screened for study participation. 135 subjects satisfied eligibility criteria, and 103 subjects (18-41 years of age) were randomized for vaccination to assure that ~90 subjects were eligible for challenge (allowing ~10% drop-out). Randomization by group yielded: FluMist - n=36, TIV – n=33, and placebo – n=34 subjects. The mean age in each of the study groups was ~ 25 years and ~74% of subjects were male. The ethnicity was comparable between the groups

The study was designed so the challenge would include three mutually exclusive groups of ~30 serosusceptible subjects. Some subjects in a group were serosusceptible to one or both of the other strains. Of note, though all participants enrolled in the vaccine phase of the protocol were serosusceptible (HAI $\leq$ 1:8) to at least one strain at screening, seven subjects challenged with A/H3N2 and nine subjects challenged with type B had HAI titers $\geq$ 1:16 on Day 0 (vaccination day). The sponsor attributed this, in part, to assay variability.

Efficacy Results

Primary Efficacy Endpoint

The primary measure of protective efficacy of FluMist was the difference between the rates of laboratory-documented influenza illness in the FluMist and placebo groups, shown in Table 3.2.2b. For this analysis for all participants (whether or not they were serosusceptible at screening), 2/29 (7%) of FluMist, 4/32 (13%) of TIV, and 14/31 (45%) of placebo had cases of laboratory documented illness. Compared to placebo, the protective efficacy of FluMist was

85% (28, 100) with p=0.001 and TIV was 71% (2, 97) with p=0.006; Mantel-Haenszel test stratified by strain. The study was not large enough to produce precise estimates of strain-specific efficacy. The efficacy rates between FluMist and TIV were not statistically different.

Table 3.2.2.b AV003 – Percent Protective Efficacy of FluMist and TIV Relative to Placebo by Serotype for All Challenged Participants with HAI Titers < 1:8 on Day 0.

	Viral Shedding %	4-Fold Rise in HAI Titers[a] %	Infection[b] %	Respiratory Illness %	Any Illness[c] %	Laboratory-confirmed influenza Illness[d] %
H1N1						
FluMist	40	60	49	14	14	80
TIV	60	100	66	31	31	60
H3N2						
FluMist	-50	67	33	75	75	83
TIV	-20	100	50	40	40	70
B						
FluMist	43	24	54	-14	-14	100
TIV	100	100	100	-52	-52	100
All (95% CI)						
FluMist	25 (-159,84)	52 (-52, 91)	42 (-32, 82)	31 (-58, 76)	31 (-58, 76)	84 (16, 100)
TIV	51 (-94, 93)	100(21, 100)	68 (9, 95)	11 (-96, 60)	11 (-96, 60)	69 (-9, 97)

A negative protective rate means the incidence in vaccinees was higher than in placebo recipients.
[a] Missing 4 participants: 2 H1N1-challenged placebo recipients and 2 TIV-challenged subjects
[b] Defined as viral shedding on any day and/or > 4-fold rise in HAI antibody to the challenge strain (missing 2 TIV-challenged subjects missing 4-fold rises in HAI titers).
[c] Respiratory illness, systemic illness or febrile illness.
[d] Defined as any influenza illness and infection (missing 1 of the 2 TIV group missing 4-fold rises in HAI titers).
Table from MedImmune, Original BLA October 2000, Volume 12.

Viral Shedding

Three FluMist, two TIV and seven placebo recipients shed virus for more than one day post-challenge with wild type strain, and these were not statistically significantly different. Compared to placebo, FluMist was 25% (95% CI: -159, 84) protective against viral shedding and TIV was 52% (95% CI: -77, 94) protective. Compared to placebo, FluMist was 54% (95% CI: -41, 91) protective as denoted by > 4-fold rises in HAI titers, while TIV had 100% (95% CI: 32, 100) efficacy. These results were not different when the evaluations were performed including only the serosusceptible subjects.

AV003 - Summary

In this trial in healthy adults, protection against influenza illness following challenge with wild-type strains of influenza was demonstrated following FluMist for all strains combined. However, the study was not large enough to produce precise estimates of strain-specific protection for each wild-type strain (A/H1N1, A/H3N2/ B).

Overall Summary Efficacy and Effectiveness

Efficacy has been demonstrated against culture-confirmed influenza illness caused by circulating strains of A/H3N2 and B after one or two doses of FluMist in healthy children 15 through 71 months in Year 1, and after re-vaccination in Year 2. Efficacy was also demonstrated for children in the age subgroup of 60 months through 71 months of age; these are the only efficacy data for children 60 months through 17 years of age. No efficacy or effectiveness data are available for children ages 6 through 17 years.

No field efficacy data are available for A/H1N1 following FluMist in any age group. In children previously immunized with FluMist, protection against shedding was demonstrated following intranasal challenge with the same monovalent vaccine strain A/H1N1. A small number of adults were challenged with wild-type strain A/H1N1 after FluMist administration; however, the study was not large enough to produce precise estimates of strain-specific protection from challenge.

Effectiveness was not demonstrated following FluMist in healthy working adults, ages 18 years through 64 years against the primary endpoint, any febrile illness. Effectiveness was demonstrated against the occurrence of severe febrile illness and febrile URI, as well as against CDC-ILI (post-hoc).

In subgroup analyses among individuals $\geq$ 50 years through 64 years of age, no decrease following receipt of FluMist was observed for any febrile illness, severe febrile illness, febrile URI or CDC-ILI. These analyses were not planned prospectively, and the study was not sufficiently powered to demonstrate effectiveness in this older age group.